Quality of prescribing in chronic kidney disease and type 2 diabetes

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General introduction

1

Prevention and treatment of diseases and disease complications are central in healthcare. Evidence-based clinical guidelines describe certain processes of healthcare, including diagnosing, monitoring and treating patients. These guidelines are based on previous research showing the benefits and risks of these processes of care and, in absence of scientific evidence, clinical expertise or opinions. To evaluate whether guidelines are followed and to assess the quality of healthcare, quality indicators are used. These indicators can be used both for internal and external evaluation.[1] Quality indicators can be classified into structure, process and outcome indicators.[2] Structure indicators focus on organizational aspects, such as staff availability, equipment and policies. Process indicators focus on the actual care delivery, such as the conduct of physical examinations, laboratory measurements and prescribing. Outcome indicators focus on these health outcomes, such as risk factor levels, disease complications or quality of life. Structure aspects can influence the likelihood of a process to occur. These processes can in turn have an influence on the health outcome of patients.

Quality of prescribing

One important process of care is the prescribing behaviour of healthcare providers. The quality of prescribing comprises of several elements. Some important elements are underprescribing, overprescribing, use of preferred drugs and medication safety.

Underprescribing means that based on guidelines, patients should (be recommended to) receive a certain treatment, but are not receiving the treatment. Overprescribing on the other hand, means that patients receive a certain treatment which is unnecessary. Moreover, some drugs are preferred over others within the same drug class, because of health benefits or economic reasons. Medication safety is an element that includes avoiding certain potentially unsafe or inappropriate drugs or dosages and avoiding drug-drug interactions.

To assess these elements of prescribing behaviour, prescribing quality indicators (PQI) are used. PQIs are ‘measurable elements of prescribing performance for which there is evidence or consensus that they can be used to assess the quality’.[3] PQIs can be drug-, disease- or patient-oriented.[4] Drug-oriented PQIs assess quality of prescribing based only on drug prescribing/dispensing data without taking into account any other aspects such as indications or comorbidities. These kinds of PQIs focus on the use of preferred drugs within a drug class or the occurrence of drug-drug interactions. Disease-oriented PQIs take into account indications and comorbidities of patients and assess to what extent the patients are under- or overprescribed with recommended treatment or whether inappropriate drugs are prescribed. Patient-oriented PQIs go a step further and take into account patient-specific information such as age and severity of the disease to assess treatment suitable for a specific patient.

As with all quality indicators, PQIs must be validated before being used in daily practice. Several types of validation are considered essential, including content, face, operational and predictive validity.[5] Content validity reflects whether the definitions of the PQI correctly follow clinical guidelines. Face validity reflects whether a group of experts in the field accepts the PQI as being valid. Using an expert panel representative of the field during the development stage of the indicators will assure face validity. Operational validity reflects whether the PQIs can be measured using available data from clinical practice. Finally, predictive validity reflects whether the PQI is predictive of a relevant clinical outcome. In other words, calculating PQIs with predictive validity and improving on the PQI scores is beneficial for the patient. This can be shown when there is a positive relationship between better PQI scores and improved intermediate or hard clinical endpoints. Previous research has shown that using PQIs to give feedback to the healthcare providers has led to increased quality of prescribing.[6]

Chronic kidney disease

Chronic kidney disease (CKD) is a condition with a potentially high burden of disease.[7] Clinical guidelines for CKD recommend monitoring of disease progression and factors such as kidney function, blood pressure and albuminuria.[8-11] In addition, these guidelines include recommendations on treatment with blood pressure and albuminuria lowering drugs, statins, and phosphate binders. Furthermore, several types of drugs should be avoided in certain situations. Adhering to these guidelines should reduce the risk of end-stage renal disease, cardiovascular morbidity and mortality, but also the risk of adverse drug reactions.

In CKD care, assessing the quality of care is relatively new with few quality assessment initiatives compared to fields with more experience such as type 2 diabetes. Previously, a set of quality indicators has been developed for CKD care[12] and some quality indicators are used in audit-and-feedback programs.[13] These quality indicators are mainly focused on monitoring kidney function and risk factor levels. Although quality of prescribing is an important aspect of quality of care, up to now only a few indicators focus on prescribing. The PQIs include disease-oriented indicators focusing on underprescribing of anaemia treatment and albuminuria lowering drugs and inappropriate prescribing of non-steroidal anti-inflammatory drugs and bisphosphonates. These PQIs have been developed and validated trough a structured process,[12,14] but many areas of prescribing are still not covered. Therefore, it is evident that a comprehensive and properly validated set of PQIs to assess quality of prescribing in patients with CKD is lacking and needed.

Type 2 diabetes

Like CKD, type 2 diabetes (T2D) is a chronic condition with a potential high burden of disease, and its prevalence is increasing worldwide.[15] Clinical guidelines for T2D recommend monitoring of risk factors such as blood glucose levels, blood pressure, cholesterol levels and albuminuria.[16,17] In addition, stringent start en intensification of treatment steps for glucose, blood pressure, and albuminuria lowering drugs and statins are recommended in certain patients; furthermore, recommendations are made as well with regards to the avoidance of certain drugs in certain situations. Adhering to these recommendations should reduce the risk of developing cardiovascular, renal and other diabetes complications and mortality as well as reduce the risk of adverse drug reactions.

The development of quality indicators for T2D started in the 1990s.[18] Since then, many quality indicators have been developed, validated and used in audit-and-feedback programs. Most quality indicators to assess quality of T2D care are focused on monitoring risk factors and achieving target levels, whereas few focus on the quality of prescribing.[19] Previously, specific PQIs have been developed to assess quality of prescribing in patients with T2D.[20] These PQIs focus on prescribing glucose, blood pressure and albuminuria lowering drugs, statins and acetylsalicylic acid, but none of the PQIs focus on medication safety. Moreover, quite often, such PQIs have not been implemented in practice nor updated to the most recent guidelines and recommendations.

PQIs have different structures with regard to the time aspect; most of the currently used PQIs are cross-sectional indicators, using data from one point in time to assess quality of prescribing. On the other hand, some of them are clinical action indicators, i.e. whether healthcare providers act adequately in patients with elevated risk factor levels. These indicators “award” actions of healthcare providers when the patient reaches a target level with or without clinical action, or when the healthcare provider takes the appropriate clinical action, while excluding patients for whom the action is inappropriate.[18,21] Clinical action indicators are patient-oriented indicators and have shown to be more clinically meaningful than cross-sectional indicators.[22] These clinical action indicators also fit into the current views on individualizing healthcare.[21] Previous research showed that improvements in clinical action indicators for treatment of T2D were also associated with better patient outcomes.[23,24] A new and updated set should therefore incorporate individualized care, including the preferred clinical action indicators whilst also taking into account patient differentiation.

Research aims and outline of the thesis

PQIs are the central focus of this thesis. The thesis will describe different aspects of the development, validation and application process of PQIs. The aim of the first part of this thesis is to provide an overview of existing process quality indicators for CKD care, and to develop a new set of PQIs for CKD care. This set will be tested for content, face and operational validity and applied to assess the current quality of prescribing in CKD care.

The aim of the second part of this thesis is to develop and validate a new set of PQIs for T2D care. Besides the testing for content, face and operational validity, the second part will also focus on testing the predictive validity of the newly designed PQIs. With these sets, the current quality of prescribing in CKD and T2D care can hopefully be assessed. This information, when validated as being of consequence, can in turn be used in audit-and-feedback programs to identify priority areas of improvement and improve the quality of prescribing.

Part I: Quality of prescribing in chronic kidney disease

Chapter 2 presents a systematic literature review of studies focusing on process quality indicators for CKD care. The objectives of this review are to (I) identify existing quality indicators intended for assessing processes of care in patients with CKD and (II) identify the quality indicators that have sufficient content, face, operational and predictive validity. **Chapter 3** describes the development and operational validation of a set of PQIs for CKD care. The set is developed by means of a structured process based on clinical guidelines and expert experience. After development, the set is tested for operational validity in patients with CKD using a large database of primary care patients with T2D, the Groningen Initiative to Analyse Type 2 diabetes (GIANTT). In **chapter 4**, this set of PQIs for CKD is used to assess the quality of prescribing in outpatient clinics in the Netherlands. This study uses data from two academic and one non-academic clinics. In particular, differences in quality of prescribing among different stages of CKD and different clinics are examined.

Part II: Quality of prescribing in type 2 diabetes

Chapter 5 describes the development and operational validation of a set of PQIs for T2D care. In addition to PQIs focusing on current prescribing, also clinical action indicators focusing on the start and intensification of treatment are included in this set. This set is also developed using a structured method based on clinical guidelines and expert experience. For operational validity testing, the GIANTT and Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) databases are used. In **chapter 6**, several of the developed PQIs are tested on possible associations with intermediate patient outcomes. The focus of this chapter is on the clinical action indicators regarding timely start and intensification of glucose, blood pressure and albuminuria lowering drugs and statins and the clinical outcomes glycated haemoglobin, systolic blood pressure, albuminuria and low-density lipoprotein-cholesterol. The association between guideline-adherent prescribing and health-related quality of life is assessed in **chapter 7** using data from the e-Vita/ZODIAC study. In this chapter, besides PQIs focusing on current use of albuminuria lowering drugs and statins, PQIs on medication safety are also tested. In addition, the association between medication burden en health-related quality of life is assessed.

Finally, the main findings of these studies are discussed in light of their implications for research and clinical practice in **chapter 8**.

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Part I

QUALITY OF PRESCRIBING IN CHRONIC KIDNEY DISEASE

Process quality indicators for chronic kidney disease risk management: a systematic literature review

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Abstract

Background: Quality indicators (QIs) can be used for measuring the quality of actions of healthcare providers. This systematic review gives an overview of such QIs measuring processes of care for chronic kidney disease (CKD), and identifies the QIs that have content, face, operational and/or predictive validity.
Methods: Pubmed and Embase were searched using a strategy combining the terms ‘quality of care’, ‘quality indicators’ and ‘chronic kidney disease’. Papers were included if they focused on developing, testing or applying QIs for assessing the quality of care in adult patients with CKD not on renal replacement therapy.
Results: Two hundred and seventy-three QIs from thirty-one papers were extracted, including QIs on adequate monitoring of kidney function and vascular risk factors, on indicated treatment, drug safety, adherence and referral to a specialist. The QIs that were considered content, face and operational valid focused on monitoring of glomerular filtration rate, albumin-creatinine ratio, lipid levels and blood pressure, the use of non-steroidal anti-inflammatory drugs, nitrofurantoin and bisphosphonates in patients with CKD, and QIs on monitoring haemoglobin and treatment with angiotensin-converting-enzyme inhibitors/angiotensin-II-receptor-blockers in patients with CKD and comorbidities. No QIs were tested for predictive validity. In addition, only two QIs focused on diet and no other QIs focused on lifestyle management.
Conclusions: Based on this review, sufficiently validated QIs can be selected for measuring the quality of CKD care. This review provides insight in QIs that need further validation, and in areas of care where QIs are still lacking.

Introduction

Previous studies showed that the quality of processes of care in patients with chronic kidney disease (CKD) is not optimal with regard to monitoring of risk factors and risk factor management, in particular prescription of drugs.[1-4] Quality indicators (QIs) can be helpful for giving feedback to healthcare providers, and in quality assurance and improvement programs. The use of QIs can lead to better quality of care and, hence, fewer complications and hospitalizations.[5] In order to be relevant, useful and acceptable for the healthcare providers, these indicators should be properly developed. Ideally, QIs should have sufficient content, face, operational and predictive validity.[6,7] Content validity represents whether the QIs are underpinned by evidence, either from clinical guidelines or scientific evidence. Face validity reflects whether a group of experts in the field accepts the QIs as sufficiently valid and accurately measuring quality. Operational validity or feasibility means that the QIs can be measured using the routinely collected data from clinical practice, thus preventing the need of double or extra registration effort and burden.[6,8] Predictive validity means that the QI can be seen as an intermediate parameter, which is predictive of a relevant clinical outcome. Especially when QIs are used for external purposes, such as in a pay-for-performance programme, evidence is needed that the measured care leads to better patient outcomes.

This review focuses on QIs measuring processes of care in patients with CKD. Such process indicators reflect the quality of actions of healthcare providers, such as whether tests are performed or treatment is prescribed as recommended by the guidelines.[9] Several sets of QIs for patients with CKD have previously been developed by individual research groups[10] or by quality improvement organizations, such as the UK Quality Outcomes Framework (QOF)[11] and the US Renal Physicians Association (RPA).[12] To our knowledge, an overview of the developed QIs and their validity is lacking. Such an overview will be useful to support a proper selection of relevant and sufficiently validated QIs and the development of QI sets for CKD care on national and international level.[13] Therefore, the aims of this review are (I) to identify the existing QIs intended for measuring processes of care in patients with CKD, and (II) to identify the QIs that have sufficient content, face, operational and predictive validity.

Methods

Search strategy

We searched Pubmed and Embase for papers using a strategy combining the terms 'quality of care', 'quality indicators' and 'chronic kidney disease' excluding kidney cancer (Appendix 1, Table S2.1). We used both MeSH/Emtree terms as well as free text terms in the title, abstract and keywords and there was no restriction on publication year. A snowballing procedure was used to find papers not covered by our search strategy.

Study Selection

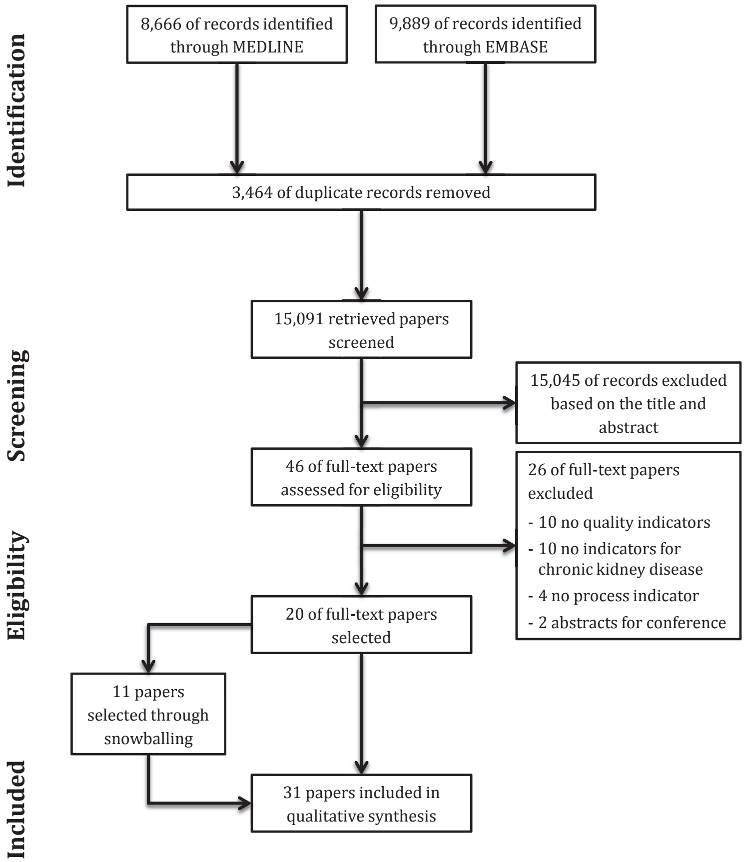
The papers were included when they focused on (I) developing QIs, or (II) testing the validity of QIs, or (III) applying QIs to measure the quality of processes of care in a population of adult patients with CKD not on renal replacement therapy. Two researchers (GS, KS) screened the titles and abstracts of the retrieved papers and selected relevant papers. Next, the full text of the selected papers was read by both researchers to determine whether the papers were eligible for inclusion (Figure 2.1). Disagreement between reviewers was resolved through discussion.
The included papers were described in terms of general characteristics, which were aim, design of study, setting and number of QIs. The QIs from the papers were retrieved and classified according to the measured process of care aspects, including monitoring, pharmacotherapy, drug safety, medication adherence and referral. The data were extracted by one author (KS) and checked by two authors (GS, PD) using a structured data collection form. Disagreement was resolved through discussion.

Furthermore, the type of validity assessed was recorded, distinguishing content, face, operational and predictive validity (Table 2.1).

Table 2.1: Types of validity

Type of validity	Explanation
Face validity	Indicators are assessed and accepted by a group of experts or professionals in the field
Content validity	Indicators are based on literature review or evidence-based clinical guidelines
Operational validity	Feasibility of reliable calculation of indicators is demonstrated or defended in the view of available data
Predictive validity	Indicators are associated with clinical patient outcomes

Figure 2.1: Flow diagram of selection process of the included studies



Validity of quality indicators

For content validity, the following classes were defined: (I) unknown when the source of QIs was not adequately described, (II) inadequate when evidence underlying the QI was assessed as insufficient by the authors, (III) adequate when QIs were derived by the authors from evidence-based recommendations, or (IV) adequate when QI were previously derived by others from evidence-based recommendations. For face, operational and predictive validity, the following classes were defined: the QI was (I) not tested, (II) not adequately tested, (III) adequately tested but not valid, (IV) adequately tested and valid, or (V) previously adequately tested and valid. The QIs presented in the papers were considered to be adequately tested for face validity when an expert panel consisting of representatives in the field followed a structured assessment procedure and accepted the QIs as valid. The QIs were considered adequately tested for operational validity when they were applied or tested in an appropriate patient population using routinely available data from clinical practice. The population was considered appropriate when it was representative of the target population with regard to age and CKD stage. The data source used for testing the operational validity was scored with 'A' for electronic medical records or administrative data, 'B' for medical chart reviews or 'C' for self-reported data, where A implies that the QIs could be calculated using routinely available data. Finally, the QIs were considered adequately tested for predictive validity when an association was tested with a relevant patient outcome in an analysis adjusting for possible confounders.

Results

We searched in Pubmed (n=8,666) and Embase (n=9,889) up to 31 December 2015 and identified a total of 15,091 papers after removing the duplicates. After title and abstract screening and additional snowballing, a total of 51 papers remained for full text analysis. Thirty-one studies were eligible for inclusion in the review.

General characteristics

Of the 31 papers, three papers focused on developing QIs, four papers focused on testing QIs and 24 studies focused on assessing the quality of care using QIs (Table 2.2).

All papers provided information to classify content validity, nine papers provided information to assess face validity, and 28 papers provided information to allow assessment of operational validity. There were no papers on predictive validity (Table 2.2). Fifteen papers were based on studies conducted in the US, nine in Europe, four in Canada and three in Asia. In total, 273 QIs were identified. The median number of QIs per paper was 6 (interquartile range of 2-11). More than half of the papers (n=18) were published in the last 5 years (2011-2015). Twenty-nine papers included QIs that measured appropriate pharmacotherapy, eighteen papers included QIs that measured adequate monitoring of kidney function or risk factors, six papers included QIs on drug safety issues, five papers included QIs on referrals and one paper included QIs on medication adherence (Table 2.2). Furthermore, all but one QI were designed in a cross-sectional manner, meaning that they measure the quality of care at one point in time and do not take into account previous measurements or prescriptions. The longitudinal QI focused on the lack of intensification of antihypertensive therapy.[14]

Table 2.2: Characteristics of included papers, including assessment of quality of content, face, operational and predictive validity of quality indicators in the papers

			Type of indicators					**Type of validity**				
Study	**Number of indicators**	**Aim**	**Monitoring**	**Treatment**	**Drug safety**	**Adherence**	**Referral**	**Content**	**Face**	**Operational**	**Data source**	**Predictive**
Allen *et al.*, 2011[3]	18	Assess	√	√	√			√	0	√	A	0
Ang *et al.*, 2013[36]	8	Assess		√				√	0	√	A	0
Arora *et al.*, 2015[17]	19	Assess	√	√	√			x	0	√	A	0
Assogba *et al.*, 2012[37]	2	Assess		√				√	0	√	A	0
Bailie *et al.*, 2005[18]	8	Assess		√				x	0	√	B	0
Bellizzi *et al.*, 2010[19]	9	Assess	√	√				x/√	Ø	√	C	0
De Wet *et al.*, 2012[42]	2	Assess	√	√				+	+	√	A	0
Debenito *et al.*, 2014[41]	3	Assess	√	√				+	0	√	A	0
Desrochers *et al.*, 2011[38]	66	Develop		√	√	√	√	√	√/-	√†	B	0
Eilat-Tsanani *et al.*, 2014[20]	5	Assess	√					+/√	0/+	√	A	0
Israni *et al.*, 2003[31]	11	Assess	√	√			√	x	0	√	B	0
Jameson *et al.*, 2014[39]	13	Assess		√	√			x	0	√	A	0
Karunaratne *et al.*, 2013[21]	3	Assess		√				+/x	0/+	√	A	0
Kausz *et al.*, 2001[32]	16	Assess	√	√				x	0	√	B	0
Kuo *et al.*, 2009[35]	11	Assess	√	√				x	0	√	A	0
Litvin *et al.*, 2011[1]	3	Assess		√	√			√	0	√	A	0
Litvin & Ornstein, 201[10]	10	Develop	√	√	√		√	√	√	0	-	0
Mold *et al.*, 2014[22]	8	Assess	√	√			√	+	0	√	B	0
Murray *et al.*, 2005[33]	13	Assess	√	√				x/√	0	√	B	0
Patapas *et al.*, 2012[23]	8	Assess		√				x	0	√	B	0
Philipneri *et al.*, 2008[24]	6	Assess	√	√				√	0	√	A	0
Rucker *et al.*, 2011[25]	5	Test	√	√			√	√	0	√	A	0
Rushforth *et al.*, 2015[43]	1	Develop		√				+	√	0	-	0
Samal *et al.*, 2015[26]	8	Assess	√	√				+	0	√	A	0
Snyder *et al.*, 2009[27]	3	Assess		√				√	0	√	C	0
Thorp *et al.*, 2012[40]	1	Test	√					-	0	√	A	0
Tonelli *et al.*, 2001[30]	5	Assess		√				x	0	√	B	0
Tonelli *et al.*, 2002[14]	2	Assess		√				√	0	√	C	0
Usher-Smith *et al.*, 2007[28]	2	Test	√	√				+/√	+	√	A	0
Van den Heuvel *et al.*, 2008[29]	2	Test	√	√				+	-	0	-	0
Winkelmayer *et al.*, 2005[34]	2	Assess		√				√	0	√	A	0

Content validity: x = source of indicators is unknown/not adequately described, - = evidence underlying QI is lacking, √ = translated from guidelines by authors, + = previously developed based on guidelines. Face/operational/predictive validity: 0 = not tested, Ø = not adequately tested, - = tested but not valid, + = previously tested and validated, √ = tested and valid. Data source shown for: A = electronic medical records or administrative data, B = medical charts review, C = self-reported data. Two signs imply that the paper includes some indicators for which one sign applies and other indicators for which the other sign applies.

† Desrochers *et al*. did tested the operational validity, but also assessed the inter-rater reliability and responsiveness of the developed indicators/criteria. Reliability means that the indicator/criteria yield the same outcome when measured by different evaluators.

Different definitions for CKD were used in the papers. The majority based their definitions on the estimated glomerular filtration rate (eGFR) and stages as defined by KDIGO and KDOQI,[1,3,10,15-29] while others used creatinine clearance rate,[14,30] serum creatinine,[31-33] albuminuria/proteinuria measurements,[34] or International Classification of Diseases-codes.[35] Some studies used combinations of measurements and/or codes.[36-40] Some papers did not specify the definition of CKD but referred to guidelines using the KDOQI staging.[41-43] Most papers defined indicators for CKD stages 3-5 (Appendix 1, Table S2.2).

Validity of quality indicators on monitoring

Most QIs on adequate monitoring focus on markers for mineral and bone disorder (MBD) (24 QIs), kidney function (22 QIs), anaemia (19 QIs) and lipid levels (11 QIs) (Table 2.3).

Combining evidence on the validity of QIs with similar definitions from different studies, resulted in five general QIs on monitoring that were considered to have sufficient content, face and operational validity in at least one study. These QIs measured adequate monitoring of the eGFR,[3,10,26] albumin/creatinine ratio (ACR),[42] lipid levels,[10,24] and blood pressure in patients with CKD,[10,28] and haemoglobin levels in patients with CKD and comorbidities.[20] One QI on monitoring the complete blood count[10] was considered content and face valid but was not adequately tested on operational validity yet. The other QIs on monitoring of serum creatinine, serum albumin, serum phosphorus/phosphate, serum calcium, serum intact parathyroid hormone (iPTH), vitamin D, iron, haematocrit, anaemia, glycated haemoglobin (HbA_{1c}), body composition, diet and plasma homocysteine/C-reactive protein in patients with CKD, and on monitoring proteinuria, lipid levels, HbA_{1c} and blood pressure in patients with CKD and comorbidities were not sufficiently validated (Appendix 1, Table S2.2). Most of them were not tested on face validity, and some also lacked information on content validity. The QI on monitoring haemoglobin in all patients with CKD was assessed as lacking sufficient evidence by the authors[40] and is thus considered not content valid.

Validity of quality indicators on treatment

Most QIs on treatment focus on pharmacotherapy, including angiotensin-converting-enzyme inhibitors (ACE-i)/ angiotensin-II-receptor-blockers (ARBs) (42 QIs), other antihypertensives (18 QIs), lipid lowering drugs (18 QIs) or drugs related to anaemia (15 QIs). Combining evidence on the validity of QIs with similar definitions from different studies, one general QI was considered to have sufficient content, face and operational validity in at least one study. This QI measured treatment with ACE-i/ARBs in patients with CKD and hypertension.[21,28,36,37,42,43]

Table 2.3: Theme and definitions of extracted quality indicators

Theme of indicators	Number of indicators	Type of validity: Content	Face	Operational	Data source (A)	Predictive	Number of studies
Monitoring							
Kidney function	22	13	4	19	12	0	13
MBD	24	10	0	24	15	0	9
Anaemia	19	7	2	18	11	0	12
Lipid levels	11	6	1	10	5	0	9
HbA_{1c}	7	3	0	7	4	0	7
Blood pressure	4	4	2	2	2	0	4
Body composition	4	4	0	4	0	0	1
Diet	1	1	0	1	0	0	1
Plasma homocysteine/C-reactive protein	1	0	0	1	0	0	1
Treatment							
ACE-i/ARB	42	27	5	39	25	0	27
Other antihypertensives	18	3	2	18	8	0	11
Lipid lowering drugs	18	7	0	16	11	0	12
Anaemia related drugs	15	7	0	11	3	0	9
MBD related drugs	12	7	0	7	2	0	5
Glucose lowering drugs	4	2	0	3	0	0	3
ASA	2	0	0	2	0	0	2
Diet	2	0	0	2	0	0	1
Safety							
NSAIDs	6	5	2	5	3	0	6
Inappropriate drugs	23	23	13	20	8	0	3
Inappropriate dosages	21	21	17	17	0	0	1
Inappropriate combinations	4	4	4	4	0	0	1
Adherence							
Adherence	8	8	8	8	0	0	1
Referral							
Nephrologist	4	3	1	3	1	0	4
Other specialists	1	1	1	1	0	0	1

MBD: mineral and bone disorder; HbA_{1c}: glycated haemoglobin; ACE-i: angiotensin-converting-enzyme inhibitors; ARB: angiotensin-II-receptor-blocker; ASA: acetylsalicylic acid; NSAIDs: non-steroidal anti-inflammatory drugs.

One QI measuring treatment with ACE-i/ARB in patients with CKD, hypertension and proteinuria,[10] and two QIs measuring lack of antihypertensive treatment or too low a dose of antihypertensives[38] were considered content and face valid but were not adequately tested on operational validity. QIs focusing on treatment with ACE-i/ARBs in other patient populations, treatment with other (specific) antihypertensives, and on low protein diet were not adequately validated or assessed as not face valid (Appendix 1, Table S2.2). Furthermore, the other QIs focusing on treatment with lipid lowering drugs, erythropoietin, iron, phosphate binders, vitamin D, glucose lowering drugs, and nutritional supplements in patients with CKD were also assessed as not face valid in one study.[38]

Validity of quality indicators on drug safety

Forty out of the 54 QIs on drug safety were extracted from one paper.[38] Five other papers provided ten similar and four additional QIs on drug safety. Combined evidence on the validity of QIs measuring the use of non-steroidal anti-inflammatory drugs (NSAIDs),[1,3,10,22,38] nitrofurantoin[3,38] and bisphosphonates[3,10,38] were considered content, face and operational valid. Furthermore, several QIs were considered content and face valid but were not sufficiently validated on operational validity. They measured, among others, inappropriate use of glucose lowering drugs (2 QIs), nutritional supplements (2 QIs), anti-epileptic drugs (2 QIs), antivirals (2 QIs), antifungals (2 QIs), antibiotics (4 QIs), antigout drugs (2 QIs), inappropriate dosages for several drugs (5 QIs) and drug interactions (4 QIs). Other indicators, including indicators focusing on dosing of CKD-MDB drugs and haematopoietic drugs were assessed as not face valid in one study[38] (Appendix 1, Table S2.2).

Validity of quality indicators on medication adherence

All eight QIs focusing on medication adherence came from one paper[38] and they were found to be content and face valid (Appendix 1, Table S2.2). These QIs measure adherence to treatment for anaemia, hypertension, calcium-phosphorus metabolism, diabetes and treatment with lipid lowering drugs. The operational validity of these indicators was only tested using chart review.

Validity of quality indicators on referral

Combining evidence on the validity of three QIs with similar definitions from different studies measuring referral to a nephrologist for patients with a lower eGFR[10,22,25] was considered content, face and operational valid (Appendix 1, Table S2.2). A similar QI in a more general CKD population was not sufficiently tested.[31] Finally, one QI measuring referral for smoking cessation[38] was considered content and face valid but the operational validity was only tested using chart review.

Discussion

This systematic review gives an overview of 31 papers that developed, tested and/or applied process QIs for assessing the quality of care in patients with CKD not on renal replacement therapy. These 31 papers included 273 QIs focusing on several aspects of monitoring, pharmacotherapy, drug safety, medication adherence and referral. Only two QIs were encountered for management of protein intake but none on other lifestyle factors, such as dietary sodium restriction. Overall, the QIs that were considered content, face and operational valid focused on monitoring eGFR, ACR, lipid levels, blood pressure in patients with CKD, haemoglobin in patients with CKD and comorbidities, on undertreatment with ACE-i/ARBs in patients with CKD and hypertension, use of NSAIDs, nitrofurantoin and bisphosphonates, and referral to a nephrologist for patients with a poor kidney function. Several QIs were found to be content and face valid, but were not adequately tested on operational validity. These included QIs on monitoring of the complete blood count, treatment with ACE-i/ARBs in patients with CKD, hypertension and proteinuria, lack of antihypertensive treatment, too low a dose of antihypertensives, and a range of QIs on drug safety and medication adherence. The QIs that were found to be not valid focused on monitoring and treating of MBD and (other) anaemia risk factors, and prescribing other treatments, such as lipid lowering and glucose lowering drugs, for patients with CKD. We found no studies assessing the predictive validity of QIs.

The content validity could be assessed in all papers and 166 QIs in 22 papers were considered content valid. On the other hand, for 107 indicators evidence was not provided to support their content validity and, therefore, they cannot be implemented. These included the QIs on prescribing a low or very low protein diet for specific CKD stages. Surprisingly, only two papers adequately tested for face validity using an expert panel, resulting in 55 QIs that were considered face valid.[10,38] A substantial number of QIs on pharmacotherapy was tested and considered as not face valid in one study.[38] For certain areas, such as the drugs related to anaemia and MBD, it may be difficult to translate the recommendations in well-defined indicators, specifying the patients who are in need of such treatment.[44] In most studies (n=28), the QIs were applied to measure the quality of care, thus enabling the assessment of the operational validity. Sixteen studies used electronic medical records or administrative data, showing the feasibility of routine calculation for 108 QIs. On the other hand, in nine studies patient data were reviewed by the researchers in order to measure quality of care, thus reducing the feasibility of routine measurement. Another three studies used self-reported data, reducing the feasibility but also introducing a possible bias due to the use of potentially subjective information.

This review identifies the QIs covering various areas of CKD care. However, not all relevant areas were covered by the QIs that were content, face and operational valid. The areas that were not well covered included monitoring of MBD risk factors, anaemia risk factors, blood pressure and HbA_{1c} levels, as well as treatment of MBD, anaemia, high HbA_{1c}, and lipid levels. Furthermore, most QIs on safety were content and face valid but their operational validity was not tested for routinely available data. These areas are important for CKD care, because inadequate monitoring and treatment of these risk factors and use of inappropriate drugs might result in an increased risk of complications and disease progression.

We focused on QIs for adult patients with CKD not on renal replacement therapy. In the selected studies, various definitions of CKD were used in the QIs. These criteria were often based on the CKD stages classification according to KDOQI guideline,[16] that is, based on glomerular filtration rate. The CKD stages 1-5 represent the loss of kidney function as described in the KDIGO and KDOQI guidelines.[15,16] Mild loss of kidney function often remains unobserved, and guidelines usually focus on treatment of patients with moderate-to-severe kidney disease (stages 3-5). As a consequence, most QIs have been developed for CKD stages 3-5. There were no QIs specifically for patients with CKD stage 1 and 2. For some indicators the CKD stage was not specified. For example, some indicators used serum creatinine levels,[31-33] or diagnostic codes[35] to identify patients with impaired renal function or CKD. Most of these indicators were not content valid nor tested on face validity. Several indicators focused on patients with elevated albuminuria levels[34,37] or with lowered creatinine clearance.[14,30,38] Such indicators were mostly content valid.

All but one of the QIs covered by this review are cross-sectional, which means they measure quality of care at a single point in time. Such indicators can be easily calculated using administrative databases. We found one longitudinal indicator, which focused on the intensification of antihypertensive treatment.[14] Longitudinal indicators require more detailed information about the timing of measurements and prescriptions (e.g. electronic health records). Such indicators have been previously developed and applied for treatment of type 2 diabetes and cardiovascular risk factors.[45-47] More attention should be given to the development and validation of longitudinal indicators for CKD care, since they have shown to give meaningful information about timeliness of treatment intensification or deintensification in other areas, such as diabetes and hypertension.[48,49]

Two papers in this review included composite measures of CKD care that consisted of multiple indicators focusing on both the process and outcomes of care.[42,43] Such composite measures can give insight in the overall quality of care. Since our focus was on quality indicators of the process of care, we did not include these composite measures in our review.

Several professional organizations developed QIs for CKD care in the past. For example, the RPA in the US developed 29 process QIs, including indicators for MBD, high blood pressure, anaemia, and dyslipidaemia management. The National Institute for Health and Care Excellence (NICE) in the UK describes fourteen process indicators in their CKD quality standard, including indicators focusing on monitoring, disease progression, cardiovascular risk, and blood pressure.[11] Furthermore, the QOF, a pay-for-performance system in the UK, uses two process QIs for CKD. When comparing our selection with those indicator sets, sixteen QIs from the RPA, five of the QIs from the NICE set, and both QIs from the QOF set were also covered by our review. These QIs focus on measuring kidney function (NICE, QOF), MBD (RPA), anaemia (RPA), lipid levels (RPA) and blood pressure (NICE, RPA), and on treatment with ACE-i/ARBs (QOF, RPA) and other antihypertensives (RPA), treatment related to anaemia (NICE, RPA) and MBD (RPA) and referral to a specialist (NICE). On the other hand, thirteen QIs from the RPA and nine QIs from the NICE were not covered by our review. This was likely due to the fact that many of the indicators focus on patients with advanced CKD and on preparing patients for renal replacement therapy. For example, QIs from the RPA that are not included in our review focus on monitoring iPTH when prescribing a phosphate binder, monitoring blood pressure when receiving erythropoietin, monitoring serum bicarbonate, prescribing elemental calcium for patients with low calcium and normal phosphorous levels, and prescribing low phosphorus diet for patients with high iPTH and/or phosphorous levels. Of note, the RPA indicators were developed fifteen years ago and are based on partly outdated guidelines.

This review has some limitations. First, although the initial search strategy identified a large number of papers, only 31 were included in the review. Therefore, the search strategy lacks specificity. During the development of the search strategy, we tried to increase the specificity of the search by making the search terms more specific. However, this led to missing papers we identified earlier as relevant for inclusion. Moreover, there is no standard for scoring the validity of the indicators. Therefore, we created our own scoring system for assessing the content, face and operational validity of the indicators. We based our choices on definitions provided previously.[6] Second, we summarised the information about the validity of QIs that came from different studies. For this, we combined the evidence on the validity of indicators with similar definitions. What is considered similar, however, is a matter of judgment.

To our knowledge, this is the first overview of QIs for CKD care that measure the actions of healthcare providers. The QIs that are considered content, face and operational valid focus on adequate monitoring of eGFR, lipid levels and blood pressure, on (under)treatment with ACE-i/ARBs, on use of NSAIDs, nitrofurantoin and bisphosphonates. This selection can be helpful for giving feedback to healthcare professionals to learn about their clinical practice. Further development and validation is needed to cover other areas that are relevant for CKD care, such as management of lifestyle factors.

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Development and initial validation of prescribing quality indicators for patients with chronic kidney disease

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Abstract

Background: Quality assessment is a key element for improving the quality of care. Currently, a comprehensive indicator set for measuring the quality of medication treatment in patients with chronic kidney disease (CKD) is lacking. Our aim was to develop and validate a set of prescribing quality indicators (PQIs) for CKD care, and to test the feasibility of applying this set in practice.
Methods: Potential indicators were based on clinical practice guidelines and evaluated using the RAND/UCLA Appropriateness Method. This is a structured process in which an expert panel assesses the validity of the indicators. Feasibility was tested in a Dutch primary care database including more than 4,500 diabetes patients with CKD.
Results: An initial list of 22 PQIs was assessed by twelve experts. After changing ten PQIs, adding two and rejecting eight, a final list of sixteen indicators was accepted by the expert panel as valid. These PQIs focused on the treatment of hypertension, albuminuria, mineral and bone disorder, statin prescribing and possible unsafe medication. The indicators were successfully applied to measure treatment quality in the primary care database, but for some indicators the number of eligible patients was too small for reliable calculation. Results showed that there was room for improvement in the treatment quality of this population.
Conclusions: We developed a set of sixteen PQIs for measuring the quality of treatment in CKD patients, which had sufficient content and face validity as well as operational feasibility. These PQIs can be used to point out priority areas for improvement.

Introduction

People with chronic kidney disease (CKD) have an increased risk of end-stage renal disease[1] as well as cardiovascular morbidity and mortality.[2,3] These risks can be reduced by appropriate pharmacotherapy, which is stipulated in clinical practice guidelines. These guidelines emphasize adequate treatment of hypertension, albuminuria, anaemia, mineral and bone disorder (MBD) and treatment with statins.[4-7] However, several studies have shown that the provided care is not always in line with these guidelines[8-10] and that the quality of medication treatment in patients with CKD is not optimal.[8,11,12]

Prescribing quality indicators (PQIs) are used to measure appropriate pharmacotherapy, which includes aspects of medication need, medication choice, safety, adequate dosing, optimal prescribing and adherence.[13,14] PQIs reflect the proportion of patients that received appropriate (or inappropriate) pharmacotherapy. Quality indicators can be used to monitor, compare or reward providers and provided care and can be part of a quality improvement strategy in audit and feedback programs.[15] Such audit and feedback programs can lead to an increase of the quality of medication treatment by 13%.[16]

Internationally, several quality indicator sets regarding CKD care have been developed. The American Renal Physicians Association developed a list of indicators intended to assess appropriate patient preparation for renal replacement therapy.[17] This set includes nine PQIs focusing on treatment of MBD, hypertension, anaemia and statin prescribing. Litvin and Ornstein[18] developed a set of twelve quality indicators for CKD management in primary care, three of which focused on medication treatment. A Canadian group published a list of 50 criteria that was developed for community pharmacists to assess medication safety issues and adequate medication use by patients with CKD.[19] However, none of these lists covered appropriateness of pharmacotherapy in patients with CKD. Therefore, the goal of this study was to develop a comprehensive set of PQIs for patients with CKD managed in primary or secondary care.

To develop a set of quality indicators, several steps are recommended.[20,21] First, an initial list of indicators should be generated based on literature, clinical guidelines and expert consultation. Second, the content and face validity of the indicators should be assessed. Content validity represents whether these indicators correctly reflect the recommendations from clinical guidelines, whereas face validity represents whether a group of experts in the field accept the indicators as measuring quality of care. Next, the operational validity of the indicators should to be tested. Operational validity represents the feasibility to calculate the indicators in a reliable way, preferably using routinely collected data.[15] Following these recommendations, our specific aims were to develop a set of PQIs for monitoring CKD care that is both content and face valid and to test the operational validity of the indicators.

METHODS

Selection of indicators

An initial list of PQIs was developed based on existing national[4,22-24] and international guidelines[5-7,25-31] and literature.[32-34] Recommendations with level A or B evidence according to the national guidelines for medication treatment were extracted and converted in potential PQIs by three members of the research team. This first list of potential indicators was discussed with an experienced clinician to refine the indicator definitions. Next, the list was discussed with three patient representatives to ascertain that all relevant topics from the patient perspective were included.

Content and face validation

To assess the content and face validity of the indicators, the RAND/UCLA Appropriateness Method (RAM) was used.[35] This is a three-round modified Delphi method that combines evidence with expert opinion and consensus and is considered an appropriate method for assessing the validity of indicators.[36] Since we intended to assess the face validity of the PQIs for primary and secondary care, an expert panel was formed with four experts from each of three relevant specialties in the Netherlands, namely nephrology, general practice and pharmacy. These were all people with a special interest or expertise with regard to the treatment of CKD patients. Financial compensation was offered to the experts for their time.

During the first round, the experts scored the indicators on three criteria using a 9-point Likert scale. Two of these criteria represent content validity, namely whether the indicator reflected the guidelines adequately ('correct reflection of guidelines') and whether the definitions were correctly formulated ('definitions'). The third criterion, whether following the indicators would result in a health gain for the patient ('health gain'), was included as a general reflection of both content and face validity. The experts received background information, including the guideline recommendations and level of evidence provided in the national guidelines. Levels of evidence were 'A' for evidence from randomized controlled trials and meta-analyses; 'B' for evidence from observational studies, case-control studies and case reports; and 'C' for expert opinion. The experts could give comments and propose changes or new indicators during the first round. The second round was a consensus meeting where the experts discussed the discrepancies and were able to change, add and remove indicators. This discussion was chaired by a moderator (PD). During the third round, the experts received the adjusted list of indicators, including explanations for the changes, deletions and additions made. This third round was similar to the first round, assessing the criteria 'correct reflection of guidelines' and 'health gain', and one new criterion, i.e. whether the indicator measured a necessary aspect of quality of care ('necessary aspect'), reflecting face validity.

Operational validity

We tested whether it was feasible to measure the selected PQIs using routinely collected primary care data. Data from the Groningen Initiative to Analyse Type 2 diabetes Treatment (GIANTT)[37] were used. The GIANTT database includes data extracted from medical records of >50,000 patients with type 2 diabetes managed in Dutch primary care. From these, we selected patients with CKD in the year 2012. CKD was defined as having an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 calculated with the chronic kidney disease epidemiology collaboration formula.[38] This corresponds to CKD stages 3-5 according to the Dutch guidelines.[4] Patients receiving renal replacement therapy were excluded from analysis. The data included information on age, gender, diabetes duration, physical examination, laboratory measurements, comorbidity and prescribed medication. Indicators were considered feasible if all indicator elements could be measured in more than 2% of patients using the available data. In addition, we calculated the minimum required number of patients for reliable comparison of indicator scores.

The Medical Ethical Committee of University Medical Center Groningen ascertained that the study does not fall under the Medical Research Involving Human Subjects Act, since it used existing anonymized data.

Statistical analysis

A PQI was considered content and face valid when (I) all criteria in the third round were rated with a median score of 7 or higher and (II) the criteria were rated without disagreement. As described in the RAM, disagreement among the experts was calculated using the ratio of the Interpercentile Range Adjusted for Symmetry over the Interpercentile Range, where a score of <1 indicates poor agreement.[35]

To assess to what extent a PQI can provide reliable scores for performance comparison, we calculated the minimum required number of patients with a moderate precision of 10 percentage points for medication need and medication choice indicators and 5 percentage points for medication safety indicators.[39] These predefined limits were arbitrary, and after observing some indicator scores below 5% we decided to conduct the calculations for such indicators using a precision level of 1 percentage point. Based on the absolute numbers, the percentages of eligible patients in our study population and the observed indicator scores, estimates for the total number of patients with CKD needed for reliable indicator scores were calculated (See Appendix 2, File S3.1).

A sensitivity analysis was conducted to test whether the indicators would yield different results when patients were selected based on two consecutive eGFR measurements. Chi-square test and where appropriate Fisher's exact test were used to compare indicator outcome scores.

All analyses were conducted using Stata version 13.1 Special Edition (StataCorp, College Station, TX, USA).

Results

Face and content validation

Indicator selection

An initial list of 22 indicators was selected and defined. Fourteen indicators focused on measuring medication need or medication choice, including three for treatment of hypertension, two for albuminuria, five for MBD, three for anaemia and one for statin prescribing. In addition, eight indicators focused on measuring medication safety and optimal prescribing and one indicator focused on measuring treatment adherence (Table 3.1). Consultation with the patient representatives did not yield any uncovered topics in our list.

First round

An expert panel was formed of four general practitioners, four nephrologists and four pharmacists working in different regions in the Netherlands. In the first round, nine indicators had one criterion, and one indicator had two criteria that were scored with uncertainty or disagreement by the experts (Figure 3.1).

Second round

Two pharmacists and one nephrologist were unable to attend the consensus meeting. The moderator voiced their comments during the meeting. Several general changes to the whole list of indicators were agreed upon. It was decided that the indicators should be restricted to patients with CKD stages 3-5 and to patients 80 years or younger except for medication safety indicators.

Table 3.1: Prescribing quality indicators with changes made during evaluation process by experts

Final indicator description; *(x) indicators in italic are not included in final set of sixteen prescribing quality indicators*	**Changes made during evaluation process**
Treatment of hypertension	
1. The percentage of patients with CKD stages 4-5 between 18 and 80 years with hypertension†, that is prescribed antihypertensives (evidence level: A) unless undesirable because of low diastolic blood pressure (<70 mmHg) (added by expert panel)	· Age restricted between 18 and 80 years · CKD stage restricted to stage 4 and 5 · Restriction of low diastolic blood pressure added
(I) The percentage of patients with CKD stages 3-5 treated with antihypertensives that is prescribed an ACE-i or ARB (evidence level: B)	Removed
2a. The percentage of patients with CKD stages 3-5 between 18 and 80 years with macro-albuminuria‡ treated with multiple antihypertensives, that is prescribed a combination of an ACE-i or ARB and a diuretic (evidence level: B)	· Age restricted between 18 and 80 years · No gender-specific albuminuria cut-off level · Restricted to macro-albuminuria
2b. The percentage of patients with CKD stages 3-5 between 18 and 80 years with micro-albuminuria‡ and diabetes§ treated with multiple antihypertensives, that is prescribed a combination of an ACE-i or ARB and a diuretic (evidence level: B)	Added · Age restricted between 18 and 80 years · No gender-specific albuminuria cut-off level · Restricted to micro-albuminuria and diabetes
Treatment of albuminuria	
3a. The percentage of patients with CKD stages 3-5 between 18 and 80 years with macro-albuminuria‡, that is prescribed an ACE-i or ARB (evidence level: A)	· Age restricted between 18 and 80 years · No gender-specific albuminuria cut-off level · Restricted to macro-albuminuria
3b. The percentage of patients with CKD stages 3-5 between 18 and 80 years with micro-albuminuria‡ and diabetes§, that is prescribed an ACE-i or ARB (evidence level: A)	Added · Age restricted between 18 and 80 years · No gender-specific albuminuria cut-off level · Restricted to micro-albuminuria and diabetes
Prescription of statins	
4. The percentage of patients with CKD stages 3-5 between 50 and 65 years, that is prescribed a statin (evidence level B for patients with high cardiovascular risk)	No changes
Treatment of MBD	

Table 3.1: Prescribing quality indicators with changes made during evaluation process by experts (continued)

Final indicator description; *(x) indicators in italic are not included in final set of sixteen prescribing quality indicators*	**Changes made during evaluation process**
5. The percentage of patients with CKD stages 3-5 between 18 and 80 years with an elevated phosphate level (>1.49 mmol/l), that is prescribed a phosphate binder (evidence level: B for control of phosphate level)	- Age restricted between 18 and 80 years - Aluminium hydroxide added as phosphate binders - For calcium-containing phosphate binders a minimal dose of >1x daily is required
(II) The percentage of patients with CKD stages 3-5 without increased phosphate that start with a phosphate binder (evidence level: B)	Removed
6. The percentage of patients with CKD stages 3-5 between 18 and 80 years treated with phosphate binders and with an elevated calcium level (>2.54 mmol/l), that is prescribed a non-calcium-containing phosphate binder (evidence level: B for control of calcium level)	- Age restricted between 18 and 80 years - Aluminium hydroxide added as phosphate binders - A correction of calcium levels for albumin is required
7. The percentage of patients with CKD stages 3-5 between 18 and 80 years treated with phosphate binders and with a low calcium level (<2.10 mmol/l), that is prescribed a calcium-containing phosphate binder (evidence level: B for control of calcium level)	- Age restricted between 18 and 80 years - Aluminium hydroxide added as phosphate binders - A correction of calcium levels for albumin is required
(III) The percentage of patients with CKD stages 3-5 with elevated PTH levels that is prescribed vitamin D (evidence level: B)	Removed
Treatment of anaemia	
(IV) The percentage of patients with CKD stages 3-5 with iron deficiency anaemia that is prescribed iron supplements (evidence level: A for control of serum haemoglobin level)	Removed
(V) The percentage of patients with CKD stages 3-5, anaemia and adequate iron supplementation that is prescribed ESA (evidence level: A for control of serum haemoglobin level)	Removed
(VI) The percentage of patients with CKD stages 3-5 without low haemoglobin or haematocrit level that is prescribed iron supplements (evidence level: B)	Removed
Medication safety	
8. The percentage of patients with CKD stages 3-5 18 years or older treated with RAAS inhibitors, that is prescribed at least two RAAS inhibitors simultaneously (dual RAAS blockade) (evidence level: A)	No changes
9. The percentage of patients with CKD stages 3-5 18 years or older with an elevated calcium level (>2.54 mmol/l), that is prescribed active vitamin D (evidence level: B for control of calcium level)	- Vitamin D restricted to active vitamin D

Table 3.1: Prescribing quality indicators with changes made during evaluation process by experts (continued)

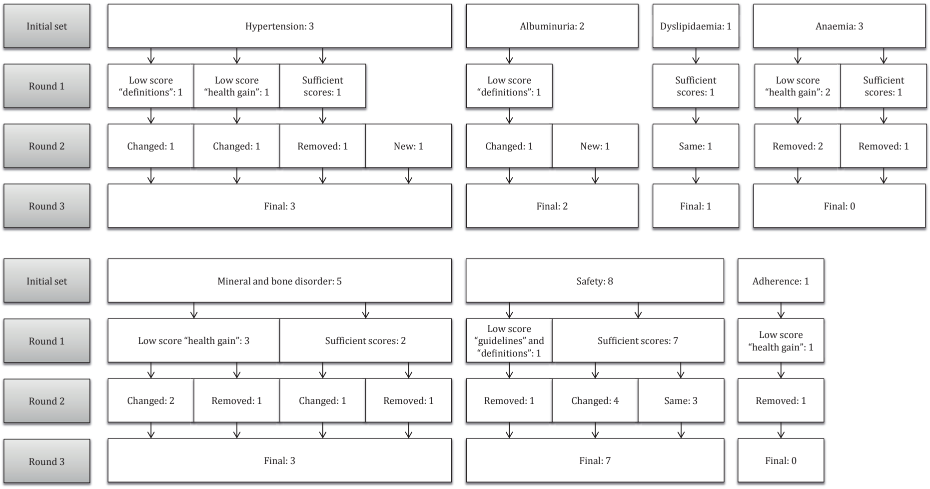
Final indicator description; *(x) indicators in italic are not included in final set of sixteen prescribing quality indicators*	**Changes made during evaluation process**
10. The percentage of patients with CKD stages 3-5 18 years or older with an haemoglobin level above target (≥7.5 mmol/l), that is prescribed an ESA (evidence level: B)	No changes
11. The percentage of patients with eGFR <30 ml/min/1.73m^2 18 years or older, that is prescribed an NSAID (evidence level: B)	- NSAIDs including also salicylic acid derivatives (carbasalate calcium) when used for analgesic, antiphlostic and/or antipyretic effect (>160mg/day)
12. The percentage of patients with eGFR <30 ml/min/1.73m^2 18 years or older with diabetes§, that is prescribed metformin (evidence level: B)	- Restricted to diabetes
13. The percentage of patients with eGFR <50 ml/min/1.73m^2 18 years or older treated with digoxin, that is prescribed high dose digoxin (>0.125 mg/day) (evidence level: B)	No changes
14. The percentage of patients with CKD stages 3-5 18 years or older, that is prescribed with a combination of NSAIDs, RAAS inhibitors and diuretics (evidence level: B)	- Restricted to stages 3 and 5 - NSAIDs including also salicylic acid derivatives (carbasalate calcium) when used for analgesic, antiphlostic and/or antipyretic effect (>160mg/day)
(VII) The percentage of patients with CKD stages 3-5 and treated with a RAAS inhibitor and a potassium-sparing diuretic simultaneously which potassium levels are measured (evidence level: B)	Removed
Treatment adherence	
(VIII) The percentage of patients with CKD stages 3-5 and treated with a ACE-i/ARB and a diuretic that is prescribed a combination pill (no evidence level)	Removed

CKD: chronic kidney disease; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; MBD: mineral and bone disorder; PTH: parathyroid hormone; ESA: erythropoiesis-stimulating agent; RAAS: renin-angiotensin-aldosterone system; eGFR: estimated glomerular filtration rate; NSAID: non-steroidal anti-inflammatory drug, including salicylic acid and derivatives.

Evidence levels: A: randomized controlled trials and/or meta-analyses; B: observational studies, case-control studies and/or case reports; C: expert opinion.

† Hypertension is defined as having a systolic blood pressure > 140 mmHg or being prescribed antihypertensives. ‡ Micro-albuminuria is defined as albumin/creatinine ratio ≥3.0 mg/mmol and <30 mg/mmol. Macro-albuminuria is defined as albumin/creatinine ratio ≥30 mg/mmol. § Diabetes is defined as either the diagnosis for diabetes or being prescribed with glucose lowering drugs.

Figure 3.1: Evaluation process of the prescribing quality indicators during the RAND/UCLA rounds



The indicator measuring medication need for statin prescribing and three of the indicators measuring medication safety scored sufficiently during the first round and remained unchanged. The lower limit of 50 years for the indicator on statin prescribing (Table 3.1, PQI 4) was debated but accepted since the overall cardiovascular risk in patients younger than 50 years without any additional cardiovascular risk factors is often too low to warrant prescribing of statins. Two of the indicators measuring medication need for hypertension, one for albuminuria, three for MDB and four safety indicators scored insufficiently in the first round and were changed during the consensus meeting (see Table 3.1). In addition, the selection of patients was adjusted for the indicator on medication need in patients with hypertension. For this indicator, all patients with an indication for treatment, meaning a diagnosis code for hypertension, an elevated level of blood pressure or a prescription for antihypertensives, were considered eligible (Table 3.1, PQI 1). Furthermore, the experts decided to differentiate two indicators for patients based on their diabetes and albuminuria status (Table 3.1, PQIs 2A/2B and 3A/3B). For the safety indicators on non-steroidal anti-inflammatory drugs (NSAIDs) prescribing (Table 3.1 PQIs 11 and 14), the experts decided to include also salicylic acid derivatives when they were prescribed in an oral dose for analgesic, antiphlostic and/or antipyretic effect (>160 mg/day). Eight indicators were discarded, including one indicator measuring medication need for hypertension, two for MBD treatment, three indicators for anaemia, one measuring medication safety and one measuring treatment adherence (Appendix 2, file S3.2).

Third round

After the consensus meeting, sixteen indicators remained; nine focusing on medication need or medication choice for hypertension, albuminuria, MBD and statin prescribing and seven focusing on medication safety (Figure 3.1). These were rated in the third round by all experts. All criteria for these indicators received a median score of 7 or higher with sufficient agreement and were therefore included for operational validity testing.

Operational validity

The indicators were validated in a cohort of 4,706 diabetes patients with CKD stages 3-5 in 2012 (Table 3.2). Operational definitions could be made for all PQIs using the available data (Appendix 2, Table S3.1). Of the sixteen indicators, ten indicators had sufficient number of eligible patients for reliable calculation in this large primary care cohort and four indicators included less than 2% of the total population (Table 3.3). Given the observed proportions and indicator outcomes, the total number of patients with CKD needed for reliable calculation would lie between 490 and 3,237 patients for the indicators focusing on medication need and medication choice for hypertension, albuminuria, and statin prescribing. For the medication safety indicators, a source population of 327 to 3,241 patients with CKD would be sufficient for reliable calculation. Reliable calculation of the scores of the MBD indicators and the safety indicators on vitamin D, digoxin and NSAID prescribing was not possible due to limited availability of phosphate and calcium levels, the low prevalence of phosphate binders, vitamin D and digoxin prescriptions and the low prevalence of patients CKD stages 4 and 5 in our population.

Indicator outcome scores for medication need and medication choice ranged from 59% for prescribing the recommended combination of an angiotensin-converting enzyme inhibitor (ACE-i)/angiotensin-II-receptor-blocker (ARB) and a diuretic in patients with CKD, diabetes and micro-albuminuria to 93% for prescribing antihypertensive medication in patients with CKD and hypertension. For the indicators on medication safety, the results ranged from 0.3% for prescribing erythropoiesis-stimulating agent in patients with normal haemoglobin levels to 21% for prescribing metformin in patients with an eGFR <30 ml/min/1.73m^2 (Table 3.3).

The sensitivity analysis did not yield different results except for the indicator on medication need for statins. Statin prescribing was higher in patients with confirmed CKD (two consecutive eGFR measurements <60 ml/min/1.73m^2) compared with patients with unconfirmed CKD (79.5% and 67.5% respectively, p=0.009).

Table 3.2 Patient characteristics at baseline

Variable	N (%)	Mean (±SD)
Age (years)	4,706 (100)	77.1 (±8.7)
Male gender	1,859 (39.5)	
Measurements		
eGFR (ml/min/1.73m^2)	4,706 (100)	47.1 (±10.3)
CKD stage		
Stage 3	4,335 (92.1)	50.5 (43.5-55.8)[a]
Stage 4	343 (7.3)	25.5 (22.0-27.8)[a]
Stage 5	28 (0.6)	11.9 (7.8-13.6)[a]
Systolic blood pressure (mmHg)	4,580 (97.3)	141.5 (±19.6)
High systolic blood pressure (>140 mmHg)	2,090 (44.4)	154 (148-165)[a]
Diastolic blood pressure (mmHg)	4,580 (97.3)	75.1 (±10.4)
Low diastolic blood pressure (<70 mmHg)	1,178 (25.0)	63 (60-66)[a]
Albumin/creatinine ratio (mg/mmol)	3,409 (72.4)	1.4 (0.0-4.9)[a]
Micro-albuminuria (3-30 mg/mmol)	884 (18.8)	7.2 (4.5-12.8)[a]
Macro-albuminuria (>30 mg/mmol)	235 (5.0)	70.4 (42.1-121.7)[a]
Phosphate (mmol/l)	156 (3.3)	1.0 (±0.2)
High phosphate level (>1.49 mmol/l)	6 (0.1)	1.6 (±0.1)
Calcium (mmol/l)	290 (6.2)	2.4 (±0.2)
High calcium level (>2.54 mmol/l)	17 (0.4)	2.6 (2.6-2.7)[a]
Low calcium level (<2.10 mmol/l)	21 (0.4)	2.1 (2.0-2.1)[a]
Haemoglobin (mmol/l)	2,264 (48.1)	8.1 (±1.0)
Low haemoglobin level (<7.5 mmol/l)	602 (12.8)	7.0 (6.6-7.3)[a]
Medication		
Antihypertensives	4,075 (86.6)	
Diuretics	2,904 (61.7)	
Beta blocking agents	2,474 (52.6)	
Calcium channel blockers	1,341 (28.5)	
Agents acting on the RAAS system	3,184 (67.7)	
ACE-i	1,937 (41.2)	
ARBs	1,360 (28.9)	
Other agents acting on the RAAS system	13 (0.3)	
Statins	2,858 (60.7)	
Phosphate binders	70 (1.5)	
Calcium containing phosphate binders	65 (1.4)	
Non-calcium containing phosphate binders	6 (0.1)	
Vitamin D	132 (2.8)	
ESA	30 (0.6)	
NSAIDs	438 (9.3)	
Metformin	2,411 (51.2)	

Table 3.2 Patient characteristics at baseline (continued)

Variable	N (%)	Mean (±SD)
Digoxin	220 (4.7)	

SD: standard deviation; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; RAAS: renin-angiotensin-aldosterone system; ACE-i: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; ESA: erythropoiesis-stimulating agent; NSAID: non-steroidal anti-inflammatory drug, including salicylic acid and derivatives.
[a] Median with interquartile range

Discussion

We developed a set of sixteen PQIs, which is intended for measuring the quality of pharmacotherapy in patients with CKD stages 3-5. The indicators are derived from evidence-based guideline recommendations and were approved by experts in the Netherlands. The PQIs focus on medication need and medication choice for the treatment of hypertension, albuminuria, MBD and statin prescribing, as well as on medication safety. Most of the indicators could be operationalized using routinely collected data from a primary care database. The number of eligible patients needed for reliable estimates was >1,250 for eleven of the indicators. To our knowledge, this is the first validated set of indicators for measuring prescribing quality in patients with CKD.

Our indicator set covers the domains medication need and medication choice for four therapeutic areas relevant for CKD patients (nine indicators), as well as the domains medication safety and optimal prescribing (seven indicators on unsafe combinations, contraindications and dosing). In contrast, previously developed indicator sets for CKD focused mainly on adequate monitoring of risk factors for CKD progression and not on medication treatment.[18] One medication indicator included in several general quality indicator sets measures ACE-i/ARB treatment in patients with albuminuria.[40,41] This indicator is also included in our PQIs set. Medication safety was extensively covered by the pharmacotherapy assessment in chronic renal disease (PAIR) criteria developed by Desrochers *et al.*.[19] However, these criteria are intended for evaluation of individual patient's treatment and have not been converted to quality indicators.

Using a medical record database that includes routinely collected data about physical examination, laboratory measurement, comorbidity and prescribed medication, we were able to make operational definitions for all indicators. To identify patients eligible for treatment, different approaches can be used.[42] In the development phase, the experts decided to apply a combination of diagnosis codes, clinical measurements and prescribed medication to identify patients

Table 3.3: Assessments in final round of RAND/UCLA method and outcomes from operational validity testing of indicators

Indicator	Final scores: Correct reflection of guidelines	Health gain	Necessary aspect
Treatment of hypertension			
1. The percentage of patients with CKD stages 4-5 between 18 and 80 years with hypertension†, that is prescribed antihypertensives unless undesirable because of low diastolic blood pressure (<70 mmHg)	8.5	8	8
2a. The percentage of patients with CKD stages 3-5 between 18 and 80 years with macro-albuminuria‡ treated with multiple antihypertensives, that is prescribed a combination of an ACE-i or ARB and a diuretic	8.5	8	8
2b. The percentage of patients with CKD stages 3-5 between 18 and 80 years with micro-albuminuria‡ and diabetes§ treated with multiple antihypertensives, that is prescribed a combination of an ACE-i or ARB and a diuretic	8.5	8	8
Treatment of albuminuria			
3a. The percentage of patients with CKD stages 3-5 between 18 and 80 years with macro-albuminuria‡, that is prescribed an ACE-i or ARB	9	9	9
3b. The percentage of patients with CKD stages 3-5 between 18 and 80 years with micro-albuminuria‡ and diabetes§, that is prescribed an ACE-i or ARB	8.5	8.5	8.5
Prescription of statins			
4. The percentage of patients with CKD stages 3-5 between 50 and 65 years, that is prescribed a statin	9	8.5	9
Treatment of MBD			
5. The percentage of patients with CKD stages 3-5 between 18 and 80 years with an elevated phosphate level (>1.49 mmol/l), that is prescribed a phosphate binder	9	8.5	8.5
6. The percentage of patients with CKD stages 3-5 between 18 and 80 years treated with phosphate binders and with an elevated calcium level (>2.54 mmol/l), that is prescribed a non-calcium-containing phosphate binder	9	8.5	8.5

Operational validity				
Outcome score (%) in study cohort	Nominator/ denominator (eligible) in study cohort	Percentage of eligible patients in total cohort (n=4,706)	N eligible patients needed for comparison	Minimal number of CKD patients needed for reliable comparison
92.9	92/99	2.1	≥26	1,238
60.5	81/134	2.8	≥92	3,237
58.9	321/545	11.6	≥93	805
81.9	122/149	3.2	≥57	1,804
78.0	495/635	13.5	≥66	490
74.3	271/365	7.7	≥74	956
75.0	39/52	1.1	≥73	6,619
-	0/0	0.0	≥96	- ¶

Table 3.3: Assessments in final round of RAND/UCLA method and outcomes from operational validity testing of indicators (continued)

	Final scores		
Indicator	**Correct reflection of guidelines**	**Health gain**	**Necessary aspect**
7. The percentage of patients with CKD stages 3-5 between 18 and 80 years treated with phosphate binders and with a low calcium level (<2.10 mmol/l), that is prescribed a calcium-containing phosphate binder	8.5	7.5	8
Medication safety			
8. The percentage of patients with CKD stages 3-5 18 years or older treated with RAAS inhibitors, that is prescribed at least two RAAS inhibitors simultaneously (dual RAAS blockade)	8.5	9	9
9. The percentage of patients with CKD stages 3-5 18 years or older with an elevated calcium level (>2.54 mmol/l), that is prescribed active vitamin D	9	8.5	8
10. The percentage of patients with CKD stages 3-5 18 years or older with an haemoglobin level above target (≥7.5 mmol/l), that is prescribed an ESA	9	9	9
11. The percentage of patients with eGFR <30ml/min/1.73m^2 18 years or older, that is prescribed an NSAID	9	9	9
12. The percentage of patients with eGFR <30 ml/min/1.73m^2 18 years or older with diabetes[§], that is prescribed metformin	9	8	8
13. The percentage of patients with eGFR <50 ml/min/1.73m^2 18 years or older, that is prescribed high dose digoxin (>0.125 mg/day)	9	8.5	8
14. The percentage of patients with CKD stages 3-5 18 years or older, that is prescribed a combination of NSAIDs, RAAS inhibitors and diuretics	9	9	9

CKD: chronic kidney disease; ACE-i: angiotensin-converting enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; MBD: mineral and bone disease; RAAS: renin-angiotensin-aldosterone system; ESA: erythropoiesis-stimulating agent; eGFR: estimated glomerular filtration rate; NSAID: non-steroidal anti-inflammatory drug, including salicylic acid and derivatives. † Hypertension is defined as having a systolic blood pressure > 140 mmHg or being prescribed antihypertensives.

3

Operational validity				
Outcome score (%) in study cohort	Nominator/ denominator (eligible) in study cohort	Percentage of eligible patients in total cohort (n=4,706)	N eligible patients needed for comparison	Minimal number of CKD patients needed for reliable comparison
-	1/1	0.0	≥96	- ¶
3.7	117/3,193	67.7	≥1,369#	2,022
17.7	3/17	0.4	≥224	-¶
0.3	5/1,662	35.2	≥115#	327
3.0	11/371	7.9	≥1,118#	14,209
21.0	78/371	7.9	≥255	3,241
11.1	16/144	3.1	≥152	4,977
4.6	216/4,706	99.8	≥1,686#	1,690

‡ Micro-albuminuria is defined as albumin/creatinine ratio ≥3.0 mg/mmol and <30 mg/mmol. Macro-albuminuria is defined as albumin/creatinine ratio ≥30 mg/mmol. § Diabetes is defined as either the diagnosis for diabetes or being prescribed with glucose lowering drugs. ¶ Not estimated due to low number of eligible patients in this cohort. # Eligible patients calculated using a precision of 1 percentage point due to low outcome of indicator.

having hypertension. Such an approach was deemed necessary since diagnosis coding in medical records is seldom complete[42-44] and a difference in quality of diagnosis registration between healthcare providers can influence the indicator scores. Also, to identify all the patients in need of a phosphate binder, both clinical measurements and prescribed medication were used. Including clinical measurements is expected to increase the sensitivity of identification of poorly treated patients,[42] whereas including patients with prescribed medication is expected to increase the sensitivity of identification of well treated patients. It is possible, however, that these medications were prescribed for other indications, reducing the specificity of the indicators and leading to overestimating their outcome.

The quality of pharmacotherapy in primary care diabetes patients with CKD was found to be suboptimal, with indicator scores <80% for prescribing ACE-i/ARBs, statins and phosphate binders when needed, and >10% for potentially unsafe prescribing of vitamin D, metformin and digoxin. PQIs are also used to compare healthcare providers. With an estimated prevalence of 4% of CKD patients in primary care,[45] most of these indicators should not be used to compare scores of individual general practitioners. Moreover, the indicators focusing on treatment of MBD and unsafe vitamin D prescribing may not be relevant for primary care, since <2% of patients from the source population were eligible. These indicators can be more relevant for a secondary care population.[17]

Of note, the level of evidence supporting some indicators is higher than for others. In patients with CKD, multiple (cardiovascular and renal) outcomes need to be considered. In addition, many large trials do not exclusively include patients with CKD. For these reasons, we included indicators based on evidence from randomized clinical trials or meta-analysis (level A) and from observational studies, case-control studies and case-report (level B). When assessing the indicators, the expert panel sometimes decided to adapt the definitions of an indicator, based on their knowledge and experience, to make them more useful for practice. For example, indicator 2b was defined during the consensus meeting to differentiate between patients with and without diabetes. As such, the indicators provide insight into prescribing for CKD patients at the level of a healthcare provider or organization but should not be seen as an evidence-based assessment of appropriate care at individual patient level. Also, the focus of our indicators is the prescribing behaviour of a healthcare provider and not the actual use of drugs by patients. This is particularly relevant for indicators that include drugs, such as NSAIDs, that are available over the counter. The PQIs are not intended to signal inappropriate use of such drugs. Furthermore, several of the safety indicators include a large group of CKD patients in the denominator, only excluding patients in whom such drug prescribing is considered safe. As a consequence, the indicator outcome can be close to 0% and appear non-informative. In such cases, the nominator may be more informative, providing the absolute number of patients who may be exposed to medication that should be avoided.

Several strengths and limitations should be considered. First, as is the case with any consensus method, the results may depend on the selected panel. Our expert panel consisted of twelve experts from three relevant disciplines, namely nephrology, general practice and pharmacy, equally represented. Our intention was to reach consensus across these disciplines on indicators intended for primary and secondary care. From general practice, we invited professionals who either contributed to the transmural guideline for the treatment of CKD or who conducted scientific research or training related to this topic. The total number of participants satisfies the requirement according to the RAM to include 7-15 experts to the panel.[35] Using more experts may impede the consensus meeting, which is an important round for making essential changes to the indicators. Per discipline, however, the number of experts was limited. Two pharmacists and one nephrologist could not attend the consensus meeting but their comments and suggestions were voiced by the moderator. All indicators were discussed, allowing for consensus, as well as indicators receiving sufficient scores in the first round. In the third round, all experts assessed the final list of indicators. Second, the indicators were based on recommendations from national evidence-based guidelines for clinical practice.[4,22-24] The recommendations in these Dutch guidelines are similar to those in other international guidelines, such as proposed by the European Renal Best Practice, the Kidney Disease Improving Global Outcomes and Kidney Disease Outcomes Quality Initiative guidelines.[5-7,25-31] This makes our indicators useful for other countries. The PQIs, however, should be updated when guidelines are updated. Thirdly, we used a single eGFR measurement to define the CKD stage. Using two measurements gives more precision in classifying the CKD stage, thereby decreasing false selection of patients for the indicators.[46] Our sensitivity analysis showed that similar outcomes were obtained for all but one indicator. Finally, we tested the operational validity of the indicators in a primary care cohort, while some of the indicators, especially those measuring medication need for MBD, may be more relevant for secondary care.

In conclusion, a set of sixteen PQIs for CKD stages 3-5 patients was developed and validated using the RAM method. The indicators focus on medication need and medication choice for hypertension, albuminuria, MBD, statin prescribing and on medication safety. The indicators can be used to point out priority areas for improvement. Due to the small number of patients with CKD stages 3-5 in a primary care practice, these indicators cannot be used for benchmarking of individual healthcare providers in primary care. At practice level, the indicators can be used for evaluation and for giving feedback to healthcare providers on the quality of prescribing. The safety indicators might also be used by healthcare providers in an alerting system. Further validation of the PQIs usefulness in a secondary care cohort is needed.

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4

Prescribing quality in secondary care patients with different stages of chronic kidney disease: a retrospective study in the Netherlands

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Abstract

Background: Insight in the prescribing quality for patients with chronic kidney disease (CKD) in secondary care is limited. The aim of this study is to assess the prescribing quality in secondary care patients with CKD stage 3-5, and assess possible differences in quality between CKD stages.
Methods: Between March 2015 and August 2016, data were collected from patients with stage 3-5 CKD seen at two university (n=569 and n=845) and one non-university nephrology outpatient clinic (n=1,718) in the Netherlands. Physical examinations, laboratory measurements and prescription data were extracted from medical records. Potentially appropriate prescribing of antihypertensives, renin-angiotensin-aldosterone system (RAAS) inhibitors, statins, phosphate binders, and potentially inappropriate prescribing according to prevailing guidelines was assessed using prescribing quality indicators. Chi-square or Fisher's Exact tests were used to test for differences in prescribing quality.
Results: RAAS inhibitors alone or with diuretics (57% respectively 52%) and statins (42%) were prescribed less often than phosphate binders (72%) or antihypertensives (94%) when indicated. Active vitamin D was relatively often prescribed when potentially not indicated (19%). Patients with high CKD stages were less likely to receive RAAS inhibitors but more likely to receive statins when indicated than stage 3 CKD patients. They also received more active vitamin D and erythropoietin stimulating agents when potentially not indicated.
Conclusions: Priority areas for improvement of prescribing in CKD outpatients include potential underprescribing of RAAS inhibitors and statins, and overprescribing of active vitamin D. CKD stage should be taken into account when assessing prescribing quality.

Introduction

Assessing quality of care in chronic kidney disease patients (CKD) is important for identifying areas for improvement. Several recent studies have shown that detection of CKD, monitoring of disease progression and metabolic parameters, and achievement of risk factor target levels are suboptimal in CKD care.[1-4] Three of these studies showed that prescribing of selected medication treatment may also be suboptimal, for example, showing potential underprescribing of renin-angiotensin-aldosterone system (RAAS) inhibitors and statins, and overprescribing of non-steroidal anti-inflammatory drugs (NSAIDs) in primary care patients with CKD. In addition, one study showed an increasing trend in prescribing of RAAS inhibitors and statins in secondary CKD patients.[5] Not much is known about differences in prescribing quality in CKD patients between healthcare organizations.

Recently, our research group has developed and validated a set of prescribing quality indicators (PQIs) for assessing the prescribing quality in patients with CKD according to clinical guideline recommendations, which has been validated in a primary care population.[6] The set is intended also for secondary care, and includes several indicators which are specifically relevant for patients with higher CKD stages. Previously it was found that with increasing CKD stages prescribing of RAAS inhibitors and NSAIDs decreased, while prescribing of phosphate binders, vitamin D and erythropoiesis-stimulating-agents (ESA) increased.[1] However, this was based on the number of prescriptions regardless of whether the medication was indicated for the included patients. The aim of this study is to assess prescribing quality in secondary care patients with CKD stage 3a-5 and differences in prescribing quality between patients with these CKD stages. In addition, we explored differences in prescribing quality between different outpatient clinics in the Netherlands.

Methods

This was a retrospective cross-sectional study assessing the prescribing quality between March 2015 and August 2016 in the Netherlands in two university nephrology outpatient clinics A and B, and one non-university nephrology outpatient clinic C. Included were patients with CKD stage 3a-5 based on estimated glomerular filtration rate (eGFR), i.e. stage 3a was defined as an eGFR ≥45 and <60 ml/min/1.73m^2, stage 3b as an eGFR ≥30 and <45 ml/min/1.73m^2, stage 4 as an eGFR ≥15 and <30 ml/min/1.73m^2, and stage 5 as an eGFR <15 ml/min/1.73m^2.[7]

Patients who received dialysis or renal transplantation were excluded from the study.

The medical ethical committee of the University Medical Center Groningen ascertained that this study using anonymized medical record data does not fall under the Medical Research Involving Human Subjects Act.

Clinics

Clinic A and clinic B are academic hospitals, which provided data from their general nephrology outpatient clinic and their predialysis outpatient clinic. Clinic C is a nonacademic hospital, which provided data from the general nephrology outpatient clinic. In all three clinics, the included CKD patients commonly visit the outpatient clinics 2-4 times per year depending on the progression of their disease. At these visits, the medication can be reviewed and changed. In all clinics, the medication included in this study is usually prescribed by the nephrologist or nephrologist in training, although other specialists or the general practitioner may also prescribe medication during the year.

Prescribing quality

A previously developed set of PQI was used for the assessment of prescribing quality.[6] This set of twelve PQIs was based on clinical guideline recommendations, and intends to provide insight in prescribing of antihypertensives, RAAS inhibitors, statins and phosphate binders when recommended (potentially appropriate prescribing) as well as prescribing of dual RAAS blockade, active vitamin D, ESA, NSAIDs, metformin, and digoxin when considered not needed or unsafe (potentially inappropriate prescribing) (Table 4.1). To specify the indicators to specific needs of patients, most indicators focus on a subgroup of the population selected based on kidney function, risk factor levels and/or age. Since there will always be individual cases for whom this is not the case, we speak of 'potentially' appropriate (or inappropriate) prescribing. Antihypertensives include diuretics, beta blocking agents, calcium channel blockers, agents acting on the RAAS system and other antihypertensives such as centrally acting agents. RAAS inhibitors include angiotensin-converting-enzyme inhibitors and angiotensin-II-receptor-blockers.

Data collection

Data were collected over twelve consecutive months at each clinic. For each patient with at least one visit to a nephrologist within the study period, the physical examination, laboratory measurement and prescription data of the most recent visit were extracted from the medical records, either by computerized or manual extraction routines. Age was determined on the visit day. For some patients, the

Table 4. 1: Indicator definitions as previously defined

Nr.	Indicator definition
Appropriate prescribing	
1	The percentage of patients with CKD stages 4-5 between 18 and 80 years with hypertension†, that is prescribed antihypertensives unless undesirable because of low diastolic blood pressure (<70 mmHg)
2	The percentage of patients with CKD stages 3-5 between 18 and 80 years with proteinuria‡, that is prescribed an ACE-i or ARB
3	The percentage of patients with CKD stages 3-5 between 18 and 80 years with proteinuria‡ treated with multiple antihypertensives, that is prescribed with a combinations of an ACE-i or ARB and a diuretic
4	The percentage of patients with CKD stages 3-5 between 50 and 65 years, that is prescribed a statin
5	The percentage of patients with CKD stages 3-5 between 8 and 80 years with an elevated phosphate level (>1.49 mmol/l), that is prescribed a phosphate binder
Inappropriate prescribing	
6	The percentage of patients with CKD stages 3-5 18 years or older treated with RAAS inhibitors, that is prescribed at least two RAAS inhibitors simultaneously (dual RAAS blockade)
7	The percentage of patients with CKD stages 3-5 18 years or older with an elevated calcium level (>2.54 mmol/l), that is prescribed active vitamin D
8	The percentage of patients with CKD stages 3-5 18 years or older and an haemoglobin level above target (≥7.5 mmol/l), that is prescribed an ESA
9	The percentage of patients with eGFR < 30 ml/min/1.73m^2 18 years or older, that is prescribed an NSAID
10	The percentage of patients with eGFR < 30 ml/min/1.73m^2 18 years or older with diabetes§, that is prescribed metformin
11	The percentage of patients with eGFR < 50 ml/min/1.73m^2 18 years or older treated with digoxin, that is prescribed high dose digoxin (>0.125 mg/day)
12	The percentage of patients with CKD stages 3-5 18 years or older, that is prescribed a combination of NSAIDs, RAAS inhibitors and diuretics

CKD: chronic kidney disease; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; RAAS: renin-angiotensin-aldosterone system; ESA: erythropoiesis-stimulating agent; eGFR: estimated glomerular filtration rate; NSAID: non-steroidal anti-inflammatory drug.
† Hypertension is defined as having a systolic blood pressure > 140 mmHg or being prescribed antihypertensives. ‡ Proteinuria is defined as > 0.5 g protein per 24h or l urine. § Diabetes is defined as either the diagnosis for diabetes or being prescribed with glucose lowering drugs.

visit date was unknown, in which case the most recent date of an eGFR assessment was used as a proxy for the visit date. The eGFR was calculated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) formula.[8] If serum creatinine was not available, the reported eGFR calculated with the MDRD formula was used. Proteinuria was defined as more than 0.5 g of protein in 24 hour or per litre urine, depending on availability.

Statistical analysis

Means with standard deviations (SD) are reported for normally distributed continuous variables, medians with interquartile ranges for non-normally distributed variables, and percentages for categorical variables. The PQI scores are presented as percentages with 95% confidence intervals. Chi-square tests or Fisher's Exact tests, in case of cell frequencies below 5, were used to test for differences in prescribing quality across different CKD stages and different clinics. P-values <0.05 were considered statistically significant. When comparing individual PQIs between CKD stages or clinics, Bonferroni correction for multiple testing was applied. Analyses were conducted using Stata version 14.2 Special Edition (Stata Corp., College Station, TX).

Results

In total, 3,132 patients with CKD stage 3a-5 were included in this study. Included patients were on average 68 years (SD: 14) old, 56% were males, the median eGFR was 35 ml/min/1.73m^2 (interquartile range: 24-46) and 16% had diabetes (Table 4.2).

Overall prescribing quality

Potentially appropriate prescribing rates varied from 94% of patients receiving antihypertensives, 57% and 52% receiving RAAS inhibitors alone or in combination with a diuretic, 42% receiving statins, and 72% receiving phosphate binders when indicated according to the guideline (Figure 4.1). Potentially inappropriate prescribing rates varied from 19% of patients receiving active vitamin D, 3% receiving ESA, 1% receiving NSAIDs, 3% receiving metformin and 4% receiving high-dose digoxin when this was possibly not needed or unsafe.

Prescribing quality across chronic kidney disease stages

Potential appropriate prescribing of RAAS inhibitors alone occurred significantly less in patients with CKD stage 5 compared to all other stages, which was also true for the combination of RAAS inhibitors and diuretics (Figure 4.2). Patients with stage 3a were less likely to receive recommended treatment with statins than patients with stage 4 or 5. Similarly, patients with stage 3b were less likely to receive statins compared to patients with stage 4. Potential inappropriate prescribing of active vitamin D in patients with elevated calcium occurred significantly less in patients with stages 3a and 3b compared to patients with stages 4 and 5. This was also the case for potentially inappropriate prescribing of ESA. Finally, poten-

Table 4.2: Patient characteristics for the whole population and separate per CKD stage

	Overall (n=3,132)	CKD 3a (n=843)	CKD 3b (n=1,125)	CKD 4 (n=862)	CKD 5 (n=302)
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Gender (males)	1,738 (55.5)	456 (54.1)	614 (54.6)	488 (56.6)	180 (59.6)
Diabetes (yes)	485 (15.5)	96 (11.4)	166 (14.8)	165 (19.1)	58 (19.2)
Clinic					
A	569 (18.2)	92 (10.9)	166 (14.8)	183 (21.2)	128 (42.4)
B	845 (27.0)	255 (30.3)	295 (26.2)	219 (25.4)	76 (25.2)
C	1,718 (54.9)	496 (58.8)	664 (59.0)	460 (53.4)	98 (32.5)
	Mean (±SD)	**Mean (±SD)**	**Mean (±SD)**	**Mean (±SD)**	**Mean (±SD)**
Age (years)	67.7 (±14.1)	63.1 (±14.2)	68.9 (±13.2)	70.2 (±13.8)	69.2 (±14.8)
eGFR (MDRD) (ml/min/1.73m^2	35 [24-46][a]	52.2 (±4.3)	37.3 (±4.2)	23.1 (±4.3)	11.1 (±2.6)
SBP (mmHg)	132.0 (±18.8)	129.4 (±17.3)	130.7 (±18.6)	133.3 (±19.4)	139.1 (±19.2)
DBP (mmHg)	75.1 (±11.2)	76.7 (±10.6)	74.9 (±11.3)	74.6 (±11.2)	74.0 (±12.1)
Total protein (g/24h urine)	0.4 [0.1-1.3][a]	0.3 [0.1-0.8][a]	0.2 [0.1-0.8][a]	0.4 [0.2-1.3][a]	1.3 [0.5-2.8][a]
Total protein (g/L urine)	0.2 [0.1-0.6][a]	0.1 [0.1-0.3][a]	0.2 [0.1-0.4][a]	0.3 [0.1-0.6][a]	0.8 [0.3-1.7][a]
Phosphate (mmol/l)	1.08 (±0.29)	0.96 (±0.20)	1.00 (±0.20)	1.10 (±0.25)	1.48 (±0.39)
Calcium (mmol/l)	2.36 (±0.14)	2.38 (±0.11)	2.37 (±0.13)	2.35 (±0.15)	2.30 (±0.16)
Haemoglobin (mmol/l)	8.0 (±1.1)	8.5 (±1.1)	8.2 (±1.0)	7.7 (±1.1)	7.0 (±0.9)

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; Clinic A and B: university nephrology outpatient clinics; clinic C: non-university nephrology outpatient clinic. [a] Median with interquartile range.

tially inappropriate prescribing of metformin in patients with an eGFR <30 ml/min/1.73m^2 was significantly lower for stage 5 as compared to stage 4.

Prescribing quality across nephrology outpatient clinics

Patients visiting the university outpatient clinics A and B were on average younger (63 years (SD: 15) and 65 years (SD: 15)) compared to those visiting the non-university outpatient clinic C (71 years (SD: 13)). Furthermore, patients visiting clinic A more often had CKD stage 4 or 5 compared to patients from clinics B and C (Table 4.2). The diabetes prevalence was higher at clinic A (26%) compared to clinic B (19%) and clinic C (10%) (Appendix 3, Table S4.1).

Significant differences were seen between clinic A and clinic C in potentially appropriate prescribing of antihypertensives, RAAS inhibitors alone, statins, and in potentially inappropriate prescribing of metformin as well as the combination of NSAIDs, RAAS inhibitors and diuretics (Figure 4.3). Furthermore, significantly more potentially appropriate prescribing of phosphate binders was seen in clinic A as compared to clinic B.

In the analyses per CKD stage (Appendix 3, Table S4.2 and S4.3), similar differences were found between the clinics. In patients with stage 3a CKD, potentially appropriate prescribing of RAAS inhibitors combined with diuretics occurred the least in clinic B. In patients with stage 3b CKD, potential appropriate prescribing of RAAS inhibitors alone or combined with diuretics occurred the most in clinic A. Patients with stage 4 CKD were significantly more likely in clinic A as compared to clinic C to receive antihypertensives and RAAS inhibitors alone. Also, patients with CKD stage 5 were more likely in clinic A as compared to clinic C to receive phosphate binders when indicated.

Discussion

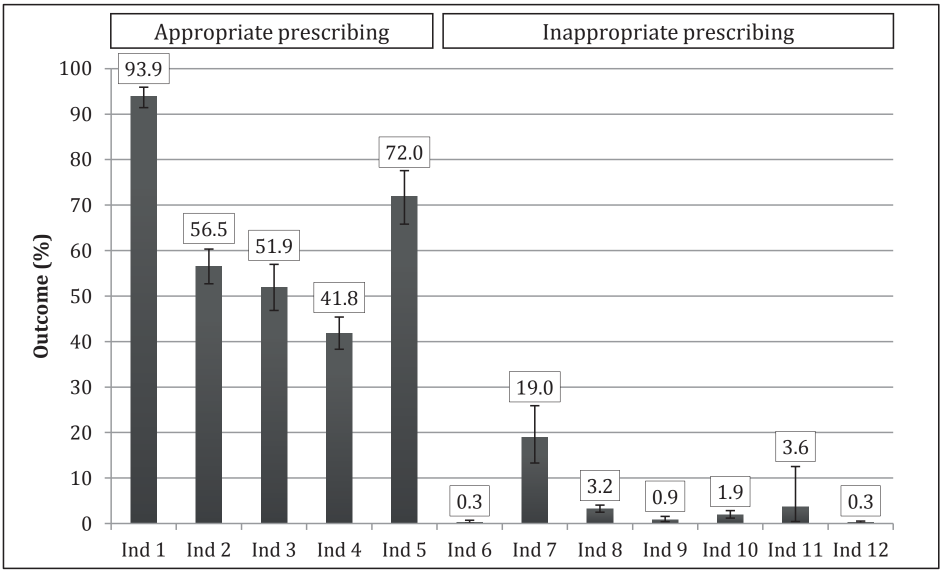
This is a first study to assess the prescribing quality in secondary care CKD patients using a broad set of PQIs and comparing different outpatient clinics. The results show that the prescribing quality varied for different therapeutic areas. RAAS inhibitors and statins were prescribed in less than 60% of the patients for whom this is potentially indicated, whereas potentially appropriate prescribing rates for antihypertensives and phosphate binders were much higher. Potentially inappropriate prescribing occurred most regarding active vitamin D. The prescribing quality also varied across different CKD stages, with decreasing potentially inappropriate prescribing of RAAS inhibitors, increasing potentially appropriate prescribing of statins, and increasing potential inappropriate prescribing of active vitamin D and ESA with higher CKD stages. Finally, significant differences were observed in prescribing between the different outpatient clinics, also after stratification for CKD stage.

Previous studies looking at the overall volume of prescribing suggested that there was underprescribing of RAAS inhibitors and statins[1,5] and overprescribing of NSAIDs[1] in patients with CKD. Our study using validated PQIs, which assess prescribing in patients for whom this is indicated, confirmed that underprescribing of RAAS inhibitors and statins are areas for possible improvement in CKD care. This was also found in a recent study among patients with stage 3-4 CKD in Canada.[3] In contrast, one older study among elderly primary care patients in Canada found relatively high prescribing rates of 75% for RAAS inhibitors and 65% for statins when recommended.[9] Regarding potentially inappropriate prescribing, that study observed a relatively high prescribing rate of NSAIDs (16%) and low prescribing rate of dual RAAS blockade (3%). Our study showed that potentially unsafe prescribing of both NSAIDs and dual RAAS blockade was uncommon in secondary care patients managed in The Netherlands. Differences in the setting are likely to influence the rates of potentially appropriate and inappropriate prescribing. This implies that the first step in quality improvement initiatives should include assessing the current prescribing quality, preferably with validated PQIs.

It was shown before that patients with higher CKD stages receive more treatment with antihypertensives, phosphate binders, vitamin D and ESA.[1,10] This can be expected because these drugs are more likely to be indicated in patients with more severe CKD. In addition, RAAS inhibitors and NSAIDs were less prescribed with increasing CKD stages.[1] These studies, however, did not take the specific indicators for treatment into account. As said before, the present study used PQIs, that identify and include patients in whom the drug treatment is either recommended or considered not needed or unsafe. We found that RAAS inhibitors were less prescribed and statins were more prescribed with increasing CKD stages. In some patients with CKD stage 5 who are in preparation of dialysis or transplantation, RAAS inhibitors may be deliberately stopped to retain the residual kidney function.[11] Lower statin prescribing rates in patients with lower CKD stages suggests that prescribers may be less aware or convinced of the need to prescribe statins in these patients. A similar pattern of less statin prescribing in patients with a higher eGFR compared to lower eGFR was observed for the elderly primary care patients in Canada[9]. In addition, we observed higher rates of potentially inappropriate prescribing of active vitamin D and ESA with increasing CKD stages. Possibly, these patients had an indication for these drugs in the past, and the decision to discontinue treatment was not yet made. Active deprescribing may be uncommon and an area for improvement in CKD care and care in general. Recently, it has been shown that there are several potential benefits of deprescribing, including better health outcomes, quality of life and cost benefits.[12] However, barriers for deprescribing have been identified, such as lack of awareness of and skills for deprescribing, devolving the responsibility to other health care providers and the complexity of polypharmacy, multimorbidity and poor communication between multiple healthcare providers.

The applied PQIs reflect general guideline recommendations and therefore a perfect score is never pursued. There can be valid reasons to refrain from prescribing according to guideline recommendations in certain patients. Valid reasons include lack of response to certain drugs, drug intolerances or patient preferences for or against certain treatment. However, guideline recommendations should guide clinical practice and are therefore useful to provide insight and monitor the quality of care. It has been argued that patient case-mix including difference in aspects, such as age or comorbidities, may explain differences in quality scores.[13] However, these may not necessarily be valid reasons for not complying with guideline recommendations. When developing the PQIs, such differences are to

Figure 4.1: Overall prescribing quality assessed with 5 PQIs for appropriate prescribing (Ind 1-5) and 7 PQIs for potential inappropriate prescribing (Ind 6 -12)

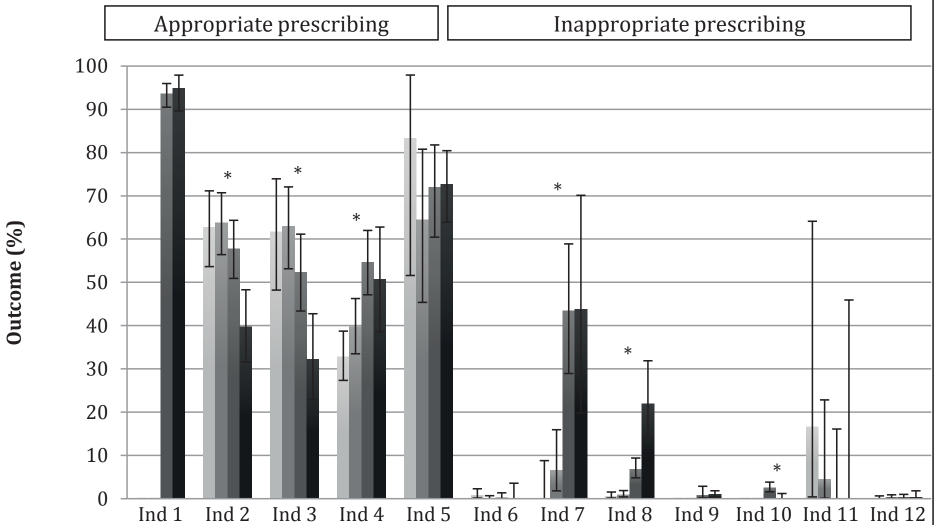


Ind 1: Patients with hypertension prescribed antihypertensives; Ind 2: Patients with albuminuria prescribed renin-angiotensin-aldosterone system (RAAS) inhibitors; Ind 3: Patients on multiple antihypertensives prescribed a combination of RAAS inhibitors and diuretics; Ind 4: Patients aged 50 to 65 years prescribed statins; Ind 5: Patients with high phosphate levels prescribed phosphate binders; Ind 6: Patients prescribed dual RAAS blockade; Ind 7: Patients with high calcium levels prescribed active vitamin D; Ind 8: Patients with normal haemoglobin levels prescribed erythropoiesis-stimulating agents; Ind 9: Patients with an estimated glomerular filtration rate (eGFR) lower than 30 ml/min/1.73m^2 prescribed high dose non-steroidal anti-inflammatory drugs (NSAIDs); Ind 10: Patients with an eGFR lower than 30 ml/min/1.73m^2 prescribed metformin; Ind 11: Patients with an eGFR lower than 50 ml/min/1.73m^2 prescribed high dose digoxin; Ind 12: Patients prescribed a combination of NSAIDs, RAAS inhibitors and diuretics. 95% Confidence Intervals were calculated based on included number of patients in the denominator of each indicator.

some extent included in the indicator definitions (e.g. age limits), thereby ensuring that the treatments are in general either recommended or inappropriate in the patients included in the indicator. Furthermore, a recent review showed that unjustified case-mix corrections can mask actual differences in quality of care.[14] Therefore, no case-mix adjustment has been made when applying the PQIs.

The results showed several differences regarding potentially appropriate as well as less potentially inappropriate prescribing between the clinics. This may in part be due to differences in the underlying patient population. The patient population from clinic A included more patients with CKD stage 5 and partly

Figure 4.2: Prescribing quality across different CKD stages (3A-5) assessed with 5 PQIs for appropriate prescribing (Ind 1-5) and 7 PQIs for potential inappropriate prescribing (Ind 6-12)

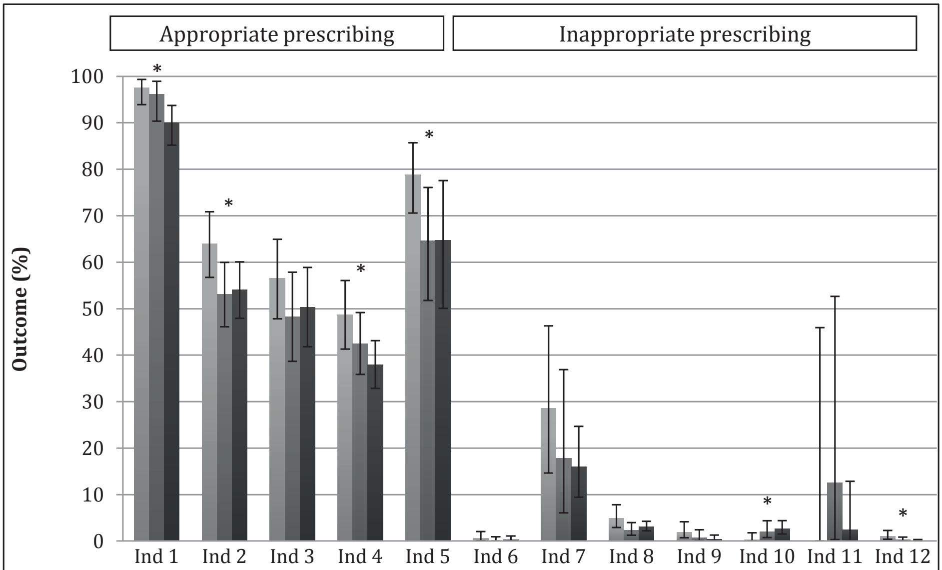


	Ind 1	Ind 2	Ind 3	Ind 4	Ind 5	Ind 6	Ind 7	Ind 8	Ind 9	Ind 10	Ind 11	Ind 12
Stage 3A		62.7	61.7	32.9	83.3	0.8	0.0	0.6			16.7	0.1
Stage 3B		63.8	63.0	39.7	64.5	0.0	6.6	1.0			4.5	0.4
Stage 4	93.6	57.7	52.3	54.6	72.0	0.2	43.5	6.8	0.8	2.6	0.0	0.3
Stage 5	94.8	39.7	32.3	50.7	72.7	0.0	43.8	22.0	1.0	0.0	0.0	0.3

Ind 1: Patients with hypertension prescribed antihypertensives; Ind 2: Patients with albuminuria prescribed renin-angiotensin-aldosterone system (RAAS) inhibitors; Ind 3: Patients on multiple antihypertensives prescribed a combination of RAAS inhibitors and diuretics; Ind 4: Patients aged 50 to 65 years prescribed statins; Ind 5: Patients with high phosphate levels prescribed phosphate binders; Ind 6: Patients prescribed dual RAAS blockade; Ind 7: Patients with high calcium levels prescribed active vitamin D; Ind 8: Patients with normal haemoglobin levels prescribed erythropoiesis-stimulating agents; Ind 9: Patients with an estimated glomerular filtration rate (eGFR) lower than 30 ml/min/1.73m^2 prescribed high dose non-steroidal anti-inflammatory drugs (NSAIDs); Ind 10: Patients with an eGFR lower than 30 ml/min/1.73m^2 prescribed metformin; Ind 11: Patients with an eGFR lower than 50 ml/min/1.73m^2 prescribed high dose digoxin; Ind 12: Patients prescribed a combination of NSAIDs, RAAS inhibitors and diuretics. 95% Confidence Intervals were calculated based on included number of patients in the denominator of each indicator.
* Significant difference between 2 or more CKD stages using Chi-square or Fisher's exact test with Bonferroni-correction for multiple testing.

pre-dialysis patients, who may be treated differently in preparation of dialysis. One would expect that this would lead to less appropriate prescribing when applying general guideline-based PQIs, but the opposite seemed to occur. Diabetes prevalence was also higher in clinic A, which may have affected prescribing. Other

Figure 4.3: Prescribing quality across different outpatient clinics assessed with 5 PQIs for appropriate prescribing (Ind 1-5) and 7 PQIs for potential inappropriate prescribing (Ind 6-12)



	Ind 1	Ind 2	Ind 3	Ind 4	Ind 5	Ind 6	Ind 7	Ind 8	Ind 9	Ind 10	Ind 11	Ind 12
Clinic A	97.6	64.0	56.5	48.7	78.9	0.6	28.6	5.0	1.9	0.3	0.0	1.1
Clinic B	96.1	53.1	48.2	42.4	64.6	0.0	17.9	2.3	0.7	2.0	12.5	0.2
Clinic C	90.0	54.0	50.4	37.9	64.7	0.3	16.0	3.1	0.4	2.7	2.4	0.1

Clinic A and B: university nephrology outpatient clinics; clinic C: non-university nephrology outpatient clinic. Ind 1: Patients with hypertension prescribed antihypertensives; Ind 2: Patients with albuminuria prescribed renin-angiotensin-aldosterone system (RAAS) inhibitors; Ind 3: Patients on multiple antihypertensives prescribed a combination of RAAS inhibitors and diuretics; Ind 4: Patients aged 50 to 65 years prescribed statins; Ind 5: Patients with high phosphate levels prescribed phosphate binders; Ind 6: Patients prescribed dual RAAS blockade; Ind 7: Patients with high calcium levels prescribed active vitamin D; Ind 8: Patients with normal haemoglobin levels prescribed erythropoiesis-stimulating agents; Ind 9: Patients with an estimated glomerular filtration rate (eGFR) lower than 30 ml/min/1.73m^2 prescribed high dose non-steroidal anti-inflammatory drugs (NSAIDs); Ind 10: Patients with an eGFR lower than 30 ml/min/1.73m^2 prescribed metformin; Ind 11: Patients with an eGFR lower than 50 ml/min/1.73m^2 prescribed high dose digoxin; Ind 12: Patients prescribed a combination of NSAIDs, RAAS inhibitors and diuretics. 95% Confidence Intervals were calculated based on included number of patients in the denominator of each indicator.
* Significant difference between 2 or all outpatient clinics using Chi-square or Fisher's exact test with Bonferroni-correction for multiple testing.

studies indicate that CKD patients with diabetes receive better quality of care in general,[15] and have higher prescription rates of RAAS inhibitors and statins.[3] This suggests that prescribing of treatment to reduce cardiovascular and renal complications gets more attention in this high risk population. Another explanation for differences in prescribing may be related to the patients' age. Patients from the non-university clinic C were on average older, which could be a reason to treat them less aggressively. In older and frail patients, life expectancy and quality of life can play an important role in decision making regarding treatment. However, all PQIs focusing on the recommended treatment with antihypertensives, RAAS inhibitors, statins and phosphate binders have an age limit which excludes a large part of these older, more frail patients.

This study assessed the prescribing quality in a cross-sectional manner, since the PQIs were defined as cross-sectional measures. This may lead to including patients who reached abnormal risk factor levels for the first time. In some cases, the healthcare provider may decide to postpone the start of treatment until a next measurement to make sure that the abnormal risk factor level persists. This also holds for discontinuation of active vitamin D in patients with elevated calcium levels and ESA in patients with normal haemoglobin levels. Furthermore, it is possible that the laboratory results became available after the visit. Therefore, the healthcare provider may not have been aware at the time of the visit that they should start or discontinue medication. In the diabetes field, it has been proposed that indicators using multiple time points may give a more accurate assessment of the prescribing quality.[16,17] Such indicators assess whether the healthcare providers start or intensify treatment when patients do not return to normal risk factor levels.

Some limitations need to be addressed. First of all, data collection methods differed for the three outpatient clinics. Data from clinic A were collected manually from electronic medical records, while data from clinic B and C were collected by computerized extraction from electronic medical records. In addition, all three clinics use different medical records systems. Although we were able to extract and combine the data in order to make comparisons possible, there were some differences in availability of measurement values. The creatinine values from clinic C were not present in the anonymized database provided for this study, making eGFR calculation impossible. However, reported eGFR calculated with the MDRD formula was available and therefore used. Furthermore, data from the physical examinations and laboratory measurements were sometimes missing, with the highest rate of missingness for clinic B (Appendix 3, Table S4.2). This could have influenced the outcome of the PQIs, since patients with unknown values were not included in the PQIs. We can only speculate why these values were missing, and how this may have influenced the assessments. It could be that the physical examinations and laboratory measurements were not performed, not recorded or lost during data extraction. Furthermore, besides diabetes, no other (cardiovascular) comorbidities have been explored to see whether the prevalence differed across patient groups.

In conclusion, using a novel set of PQIs in the present study we successfully identified several areas for improvement, including potential underprescribing of RAAS inhibitors and statins, and overprescribing of active vitamin D in secondary care patients with CKD stage 3-5. We observed differences in prescribing quality between these CKD stages and between outpatient clinics. We conclude that monitoring of the prescribing quality with PQIs is needed in secondary care to identify priority areas for improvement, and that stratification on CKD stage can be useful in quality improvement initiatives.

Acknowledgements

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Part II

QUALITY OF PRESCRIBING IN TYPE 2 DIABETES

Development and validation of prescribing quality indicators for patients with type 2 diabetes

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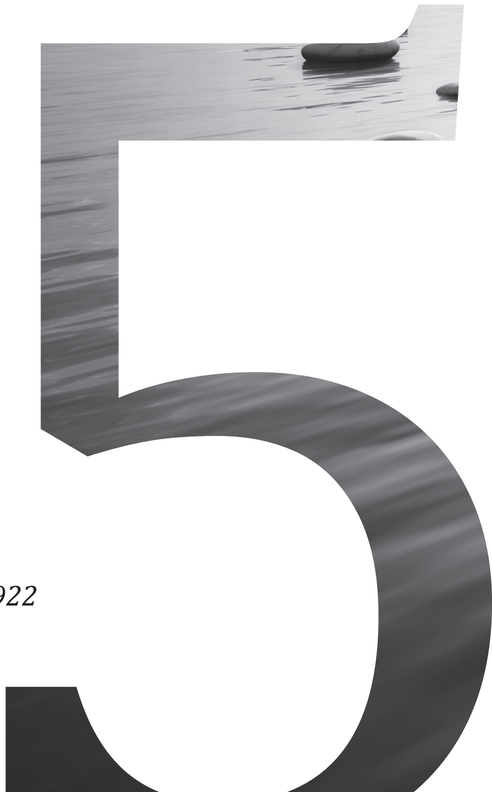

Int J Clin Pract 2017; 71(1): doi: 10.1111/ijcp.12922

Abstract

Background: Quality indicators are used to measure whether healthcare professionals act according to guidelines, but few indicators focus on the quality of pharmacotherapy for diabetes. The aim of this study was to develop and validate a set of prescribing quality indicators (PQIs) for type 2 diabetes in primary care, and to apply this set in practice. To take into account the stepwise treatment of chronic disease, clinical action indicators were specifically considered.
Methods: Potential PQIs were derived from clinical practice guidelines and evaluated using the RAND/UCLA Appropriateness Method, a modified Delphi panel. Thereafter, the feasibility of calculating the PQIs was tested in two large Dutch primary care databases including >80,000 diabetes patients in 2012.
Results: 32 PQIs focusing on treatment with glucose, lipid, blood pressure and albuminuria lowering drugs, and on vaccination, medication safety and adherence were assessed by ten experts. After the Delphi panel, the final list of twenty PQIs was tested for feasibility. All PQIs definitions were feasible for measuring the quality of medication treatment using these databases. Indicator scores ranged from 18.8% to 90.8% for PQIs focusing on current medication use, clinical action and medication choice, and from 2.1% to 37.2% for PQIs focusing on medication safety.
Conclusions: Twenty PQIs focusing on treatment with glucose, lipid, blood pressure and albuminuria lowering drugs, and on medication safety in type 2 diabetes were developed, considered valid and operationally feasible. Results showed room for improvement, especially in initiation and intensification of treatment as measured with clinical action indicators.

Introduction

Adequate medication treatment for patients with type 2 diabetes (T2D) is an integral and important part of clinical guidelines. Such guidelines emphasize treatment with glucose, lipid, blood pressure and albuminuria lowering drugs.[1,2] Furthermore, guidelines provide recommendations with regards to appropriateness and safety of medication use. Quality indicators measure whether healthcare professionals prescribe according to these guidelines. They are used to monitor quality of care, compare and reward healthcare professionals, and can be part of feedback and audit programs.[3] Earlier research using such quality indicators showed that a sizable part of the patients with T2D may receive suboptimal treatment.[4-6]

Most of the available quality indicators for T2D care measure whether risk factors are monitored and target levels are achieved, whereas few focus on the quality of prescribing.[7] Indicators focusing on prescribing are more direct measures of actions of the healthcare professionals, and can be a meaningful addition in quality assessments to support providers to prescribe appropriately.[8] The Quality Outcomes Framework (QOF) in the UK and the Healthcare Effectiveness Data and Information Set (HEDIS) in the USA only include some indicators focusing on prescribing of medication in diabetes.[9,10] In the Netherlands, the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap, NHG) and the Dutch Institute for Rational Use of Medicine (Instituut voor Verantwoord Medicijngebruik, IVM) include respectively seven and three indicators measuring the use of glucose lowering, blood pressure lowering and lipid lowering drugs in patients with diabetes.[11,12] Most of these prescribing quality indicators (PQIs) assess whether patients receive recommended medication treatment, including some focusing on current medication use and specific first-choice medication, and some focusing on medication adherence.

Other aspects of treatment can be relevant, including timely start and intensification of medication, and medication safety.[8,13] Quality indicators focusing on timely start and intensification of treatment take sequential data into account and give credit for appropriate clinical action.[14,15] Previous studies illustrated that such clinical action indicators may better reflect guideline recommendations and be more clinically meaningful than indicators that measure whether patients are treated or achieve specific targets.[14-16] Furthermore, indicators on medication safety are considered important by healthcare providers.[17] Martirosyan *et al.*[18] developed and validated a comprehensive set of thirteen PQIs for T2D, including clinical action indicators. However, these PQIs were derived from guidelines which were published more than 10 years ago, and the definitions of these PQIs required detailed clinical data that is not routinely collected for quality measurement purposes.

Therefore, the specific aims of our study are (I) to develop an up-to-date and comprehensive set of PQIs covering different aspects of treatment quality for T2D patients, (II) to assess the feasibility to calculate the PQIs using data routinely collected in primary care, and (III) to identify priority areas for improvement in T2D patients based on the PQIs estimates.

Methods

We followed the recommended steps for developing quality indicators.[19,20] We based the indicators on literature, clinical guidelines and expert consultations. A group of experts assessed the indicators. Thereafter, the feasibility to calculate the PQIs using data from actual practice was assessed.[21]

Selection of prescribing quality indicators

The initial list of PQIs was based on the current national and international guidelines.[1,2,22,23] Recommendations for medication treatment from these guidelines with level A or B evidence were extracted and converted in a list of potential PQIs by four members of the research team. This list was then discussed with an experienced clinician to refine the definitions, and with two patient representatives to ascertain that all relevant topics from the patient perspective were covered.

Content and face validation

To assess the content and face validity of the PQIs, the RAND/UCLA Appropriateness Method (RAM) was used.[24] This three-round modified Delphi method combines evidence (content validity) with expert opinion and consensus (face validity). It is considered an appropriate method for assessing the validity of indicators.[21,25] General practitioners and internists specialized in diabetes care were approached. A financial compensation was offered to the experts for their time.

During the first round, the experts individually scored the PQIs on three criteria using a 9-point Likert scale. Two of these criteria represent content validity, i.e. whether the PQI reflected the guidelines adequately (‘correct reflection of guidelines’) and whether the definitions were correctly formulated (‘definitions’). The third criterion, whether following the PQIs would result in health gain for the patient (‘health gain’), was included as a general reflection of both content and face validity. The experts could give comments and propose changes or new PQIs during the first round. The second round was a consensus meeting where the experts discussed discrepancies and were able to change, add and remove PQIs. This discussion was chaired by a moderator (PD). During the third round, the experts received a list of adjusted PQIs including explanations for the changes, deletions, and additions made. This round was similar to the first round, assessing the criteria 'correct reflection of guidelines' and 'health gain', and one new criterion, which assessed whether the PQI measured a necessary aspect of quality of care ('necessary aspect'), reflecting face validity.

Operational feasibility

The feasibility to calculate the PQIs using routinely collected data (operational feasibility) was assessed using data from the Groningen Initiative to Analyse Type 2 Diabetes Treatment (GIANTT)[26] and Zwolle Outpatient Diabetes project Integrating Care Study (ZODIAC)[27,28] databases in 2012. The GIANTT database includes longitudinal data extracted from medical records of >25,000 T2D patients managed in primary care in a region in the north of the Netherlands in 2012. The ZODIAC database includes data extracted from medical records of >55,000 T2D patients managed in primary care in regions in the east and west of the Netherlands in 2012. GIANTT includes all routinely collected data from general practices. In contrast, the ZODIAC database only includes data from the yearly visit. Both databases include structured information on age, gender, physical examination, laboratory measurements, comorbidity and prescribed medication. Age and gender were determined on 1 January 2012, while for physical examinations and laboratory measurements the most recent values in 2011 and 2012 (GIANTT) or the values from the yearly visits in 2011 and 2012 (ZODIAC) were collected. Current use of medication was defined as having a documented prescription at the yearly visit in ZODIAC, and as use of a medication at any time within the last 4 months of the calendar year in GIANTT. An indicator's definition was considered feasible when all indicator components could be calculated using the available data, i.e. the inclusion and exclusion criteria, required measurements and prescribed medication. Indicators were considered less appropriate for monitoring and benchmarking healthcare professionals when they were applicable for <2% of the total patient population. Priority areas for improvement were identified using arbitrary cut-off points of >15% for the medication safety indicator scores and <60% for all other indicator scores.

Two sensitivity analyses were performed. First, we recalculated the clinical action indicators focusing on starting and intensifying treatment including in the denominator also the patients without measurements of a risk factor (glycated haemoglobin (HbA_{1c}), low-density lipoprotein(LDL)-cholesterol, blood pressure, albumin/creatinine ratio) in the previous year. This allows for the inclusion of newly diagnosed patients for whom the risk factor measurements were not available or recorded in the database in the previous year. Second, we performed a sensitivity analysis for the GIANTT data where current use of medication was defined as use of a medication at any time in the whole year instead of the last 4 months of the year. This allows for the inclusion of patients as being treated, who did receive a repeat prescription from the practice in the latter part of the year. Two safety indicators were excluded from this sensitivity analysis, which assess medication use in relation to the last risk factor measurement in the current year. Including any use of medication for these indicators would lead to misclassification of patients whose medication was changed during the year because of the risk factor measurement.

The Medical Ethical Committee of University Medical Center Groningen ascertained that the study did not need formal approval with regards to the Medical Research Involving Human Subjects Act, since it used anonymized data from existing databases.

Statistical analysis

A PQI was considered content and face valid when (I) all criteria in the third round of the RAM method were rated with a median score of seven or more, and (II) the criteria were rated without disagreement. Disagreement among the experts was calculated using the ratio of the InterPercentile Range Adjusted for Symmetry over the InterPercentile Range, where a score of <1 indicates poor agreement.[24]

To assess to what extent a PQI can provide reliable scores for comparison of healthcare professionals, we calculated the minimum number of patients required with a moderate precision of 10 percentage points for all indicators, except for the medication safety indicators. A precision of 5 percentage points was used for safety indicators with a score of more than 5% and 1 percentage point for safety indicators with a score of 5% or less.

All analyses on expert and PQI scores were conducted using Stata version 13.1 Special Edition (Stata Corp., College Station, TX).

Results

Content and face validity

The expert panel included four general practitioners and six internists. An initial list of 32 PQIs was composed to be rated by the expert panel. This list included indicators focusing on clinical action, current medication use and medication choice for glucose (n=11), lipid (n=4), blood pressure (n=4), and albuminuria (n=3) lowering drugs. Furthermore, indicators on medication safety (n=6), vaccination (n=1), and treatment adherence (n=3) were included.

First round

In the first round, the following indicators were scored with certainty (median score≥7) and agreement: all indicators on medication safety, and all indicators on clinical action and medication choice of albuminuria lowering drugs. Furthermore, three indicators on clinical action for glucose, lipid and blood pressure lowering drugs, and one medication choice for glucose lowering drugs scored sufficient. The other nineteen indicators scored insufficient on one or more criteria (Appendix 4, Table S5.1).

Second round

Twelve PQIs were changed during the consensus meeting. For eight of these twelve PQIs, only the age restriction was altered (Appendix 4, Table S5.1, PQI **1**, **2**, **8**, **9**, **10**, **12**, **14** and *12B* [later discarded]). Regarding the other four PQIs, one was split into two indicators to differentiate between patients currently receiving or starting the recommended metformin treatment (Appendix 4, Table S5.1, PQI **5**). Another PQI was restricted to focus on patients starting with the recommended second-step gliclazide treatment (Appendix 4, Table S5.1, PQI **7**). Furthermore, the target level of blood pressure was changed from 140 mmHg to 160 mmHg in one PQI (Appendix 4, Table S5.1, PQI *12A* [later discarded]). Finally, the denominator of the PQI focusing on medication safety of simultaneous use of renin-angiotensin-aldosterone system (RAAS) inhibitors was changed from everyone into patients on RAAS treatment (Appendix 4, Table S5.1, PQI **20**).

Discarded and added indicators

The remaining fourteen indicators from the initial list were discarded. Of these fourteen, three PQIs assessing current use of different classes of glucose lowering drugs were discarded because they included all patients without addressing their need for specific treatment (Appendix 4, Table S5.1, PQI *1A, 1B, 1C*). The experts decided that these volume-based PQIs, which are included in the NHG indicator set to describe the population, did not reflect quality of care. Two PQIs focusing on clinical action for treatment of blood glucose and two PQIs focusing on clinical action for treatment of blood pressure were discarded because they focus on older patients for whom the guideline recommendations are less clear (Appendix 4, Table S5.1, PQI *4B, 4C, 15C, 17*). The PQI on simultaneous use of pioglitazone with insulin was discarded as not needed since this combination is seldom prescribed in practice (Appendix 4, Table S5.1, PQI *10*). One PQI focusing on medication choice of simvastatin was removed by the experts because the preference was not reflecting a quality of treatment aspect (Appendix 4, Table S5.1, PQI *14*). The medication safety indicator on monitoring potassium in patients with a prescription of a RAAS inhibitor or a diuretic was discarded because the indicator only assesses yearly measurements, whereas such monitoring should be conducted before and after initiation of these drugs (Appendix 4, Table S5.1, PQI *21*). Finally, the indicators focusing on vaccination and treatment adherence were discarded because they may partly reflect patient behaviour that is not under the physicians' control (Appendix 4, Table S5.1 *23*, *24*, *25*, *26*).

Four PQIs were added, including three on starting treatment with metformin, sulphonylurea derivatives (SU-derivatives) and angiotensin-converting-enzyme inhibitor (ACE-i) and one on medication safety in older patients (Appendix 4, Table S5.1, PQI **4**, 6, **16**, **19**).

Third round

The resulting list of 22 PQIs was rated again by all expert from the panel in the third round. Twenty-one of these indicators were scored sufficient on all three criteria. The new PQI focusing on starting treatment with SU-derivatives among all starters of a second glucose lowering drug, was scored insufficient on 'health gain' and therefore discarded (Appendix 4, Table S5.1, PQI 6). Furthermore, the PQIs focusing on clinical action for high blood pressure received many comments on the risk factor target levels for different age groups. Therefore, we proposed to combine both PQIs and asked the experts to rate the PQI again. This new PQI scored sufficient on all criteria (Appendix 4, Table S5.1, PQI **11**). The final list of twenty PQIs included sixteen indicators on treatment with glucose lowering (n=7), lipid lowering (n=3), blood pressure lowering (n=2), and albuminuria lowering drugs (n=4), including eight clinical action indicators, one current medication use and seven medication choice indicators, and four indicators on medication safety (Table 5.2 and Appendix 4, Table S5.1).

Operational feasibility

This final list of PQIs was then applied in the GIANTT and ZODIAC databases, including 26,321 respectively 56,808 T2D patients in 2012 (Table 5.1).
Operational definitions could be made for all PQIs using the available data (Appendix 4, Table S5.2). All indicators had sufficient number of eligible patients for reliable calculation in these large primary care cohorts (Table 5.2).

For three of the indicators, the percentage of eligible patients was less than 2% of the total population. These indicators focus on start of glucose lowering drugs, the start of ACE-i/angiotensin-II-receptor-blockers (ARBs) and the percentage

Table 5.1: Patient characteristics in 2012

	GIANTT		ZODIAC	
Variables	**N (%)**	**Mean (±SD)**	**N (%)**	**Mean (±SD)**
Age (years)	26,321 (100)	67.3 (±11.9)	56,808 (100)	67.1 (±12.0)
Male gender (%)	12,965 (49.3)		28,581 (50.3)	
Physical examination				
Systolic blood pressure (mmHg)	23,069 (87.6)	140.5 (±17.7)	45,263 (79.7)	137.2 (±16.5)
High systolic blood pressure (>140 mmHg)	9,921 (37.7)	156.2 (±13.1)	15,697 (27.6)	154.5 (±11.6)
Laboratory measurements				
HbA_{1c} (mmol/mol)	23,843 (90.6)	52.0 (±9.6)	44,731 (78.7)	50.6 (±9.9)
Elevated HbA_{1c} (>53 mmol/mol)	9,474 (36.0)	60.7 (±9.2)	13,542 (23.8)	62.0 (±9.3)
LDL-cholesterol (mmol/l)	21,259 (80.8)	2.6 (±0.9)	43,495 (76.6)	2.5 (±0.9)
Elevated LDL-cholesterol (>2.5 mmol/l)	9,669 (36.7)	3.4 (±0.7)	18,089 (31.8)	3.3 (±0.7)
Albumin/creatinine ratio (mg/mmol)	18,084 (68.7)	0.7 [0.0-1.9][a]	38,830 (68.4)	1.0 [0.4-2.3][a]
Micro/Macro-albuminuria[†]	3,265 (12.4)	7.1 [4.4-14.7][a]	7,801 (13.7)	6.2 [4.0-12.0][a]
Serum creatinine	22,271 (84.6)	78 [66-92][a]	43,888 (77.3)	77 [66-91][a]
Medication[‡]				
Glucose lowering drugs	20,267 (77.0)		36,843 (81.0)	
0	7,341 (27.9)		10,116 (22.3)	
1	11,842 (45.0)		21,882 (48.1)	
2	6,345 (24.1)		12,406 (27.3)	
3	782 (3.0)		1,040 (2.3)	
4	11 (0.0)		25 (0.1)	
5	0 (0.0)		1 (0.0)	
Insulin	3,783 (14.4)		6,734 (14.8)	
Non-insulin glucose lowering drugs	18,980 (72.1)		35,354 (77.8)	
Metformin	17,219 (65.4)		32,215 (70.9)	
SU-derivatives	7,859 (29.9)		15,299 (33.7)	
Gliclazide	5,030 (19.1)		3,034 (6.7)	
Glibenclamide	163 (0.6)		487 (1.1)	
Acarbose	9 (0.0)		30 (0.1)	
TZD	341 (1.3)		723 (1.6)	
DPP-4 inhibitors	1,168 (4.4)		1,485 (3.3)	
Other glucose lowering drugs	326 (1.2)		167 (0.4)	
Statins	17,674 (67.2)		33,095 (72.8)	
Simvastatin	10,719 (40.7)		21,835 (48.0)	
Atorvastatin	4,007 (15.2)		5,290 (11.6)	
Rosuvastatine	2,278 (8.7)		2,523 (5.6)	
Antihypertensives	20,089 (76.3)		34,560 (76.0)	
0	6,236 (23.7)		10,900 (24.0)	

Table 5.1: Patient characteristics in 2012 (continued)

	GIANTT		ZODIAC	
Variables	**N (%)**	**Mean (±SD)**	**N (%)**	**Mean (±SD)**
1	5,458 (20.7)		11,668 (25.7)	
2	6,667 (25.3)		12,098 (26.6)	
3	5,676 (21.6)		8,308 (18.3)	
4	2,150 (8.2)		2,365 (5.2)	
5	134 (0.5)		131 (0.3)	
Diuretics	12,033 (45.7)		15,495 (34.1)	
Beta blocking agents	10,725 (40.8)		18,712 (41.2)	
Calcium channel blocker	6,158 (23.4)		9,937 (21.9)	
RAAS inhibitors	15,714 (59.7)		26,155 (57.5)	
ACE-i	9,909 (37.7)		16,871 (37.1)	
ARB	6,307 (24.0)		10,499 (23.1)	
Other antihypertensives (ATC code: C02)	460 (1.8)		604 (1.3)	

GIANTT: Groningen Initiative to Analyse Type 2 diabetes Treatment; ZODIAC: Zwolle Outpatient Diabetes project Integrating Care Study; SD: standard deviation; HbA_{1c}: glycated haemoglobin; LDL-cholesterol: low-density lipoprotein-cholesterol; SU-derivatives: sulphonylurea derivatives; TZD: thiazolidinedione; DPP-4 inhibitors: dipeptidyl peptidase-4 inhibitor; RAAS: renin-angiotensin-aldosterone system; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; ATC: anatomical Therapeutic Chemical Classification System.

[a] Median and interquartile range are reported. † Micro/Macro-albuminuria is defined as an ACR ≥2.5 mg/mmol for males and ≥3.5 mg/mmol for females. ‡ For the GIANTT database, medication use in last 4 months of 2012; for the ZODIAC database, medication prescription at the yearly visit in 2012.

of patients with a low estimated glomerular filtration rate (eGFR) treated with metformin (Table 5.2).

Looking at the level of performance, several priority areas for improvement can be identified (Table 5.2). Starting with insulin scored low (38.8/42.9% for the GIANTT/ZODIAC population respectively). Furthermore, starting with statins (32.1/33.1% respectively) and intensification of statins (46.3/45.5% respectively) scored low, as did starting (56.9% in GIANTT) and intensification of antihypertensives (55.3/57.1% respectively). First-choice treatment with glicazide showed a large difference between the two populations. Finally, the medication safety indicator on use of metformin in patients with impaired kidney function (24.8/37.2% respectively of patients at risk) and potential overprescribing of glucose lowering drugs in elderly patients scored relatively high (18.2/21.3% respectively of patients at risk).

Including patients with unknown risk factor level in the previous year for the clinical action indicators resulted in including substantially more patients and also higher PQI scores for the indicators on starting treatment. The differences were especially large for the ZODIAC population (increases with more than 15% for glucose lowering drugs and more than 25% for the other starting PQIs, Appendix 4, Table S5.3A) and the PQI focusing on start with ACE-i or ARB in GIANTT (increases with more than 30%, Appendix 4, Table S5.3B). Furthermore, when measuring drugs use at any time in 2012 compared to only the last 4 months, resulted in an almost 10% higher quality score for choosing ACE-i as start medication among all starts of RAAS treatment (Appendix 4, Table S5.4, PQI 16). This shift was mainly the result of including fewer patients in the denominator (Appendix 4, Table S5.4).

Discussion

A new set of twenty indicators for measuring the quality of medication treatment in diabetes care was developed and validated. The included PQIs focus on current medication use, clinical action and medication choice for the treatment of relevant risk factors, and on medication safety. The indicators were derived from evidence-based guideline recommendation and approved by a panel of Dutch diabetes experts. All of the indicators could be operationalized using routinely collected data from two primary care databases in the Netherlands. However, some indicators may be less appropriate for monitoring and benchmarking healthcare professionals due to low numbers of eligible patients. The set of PQIs allowed identification of several priority areas for improvement, including timely start of insulin, timely start and intensification of statins and antihypertensives, prescription of metformin in patients with impaired renal function and potential overtreatment for blood glucose management in older patients.

Our set of PQIs covers a range of quality aspects, including current medication use, clinical action, medication choice and medication safety. It includes one PQI that measures current use of statins and a few PQIs on medication choice, which are similar to PQIs in existing sets. For example, the PQIs on the treatment with statins[10-12,18,29] and with ACE-i/ARBs,[9,11,12,18,29] and medication choice for glucose lowering drugs[12] are implemented in various quality assessment programs.[9,10,12] Furthermore, our set includes eight clinical action indicators, some of which were previously proposed as being more clinically relevant for physicians than indicators measuring the current medication use or achievement of specific targets.[8,14-16,30] The medication safety PQIs included in this set are new and were not

Table 5.2: Operational feasibility in GIANTT and ZODIAC database

	GIANTT		
Indicator	Outcome score(%)	Nominator/ denominator	Percentage of eligible patients
Glucose lowering drugs			
1.[†] The percentage of patients with T2D between 18 and 70 years with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that started with glucose lowering drugs or that reached the HbA_{1c} target level (≤53 mmol/mol)	73.1	174/ 238	0.9
2.[†] The percentage of patients with T2D between 18 and 70 years treated with monotherapy metformin and with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that is intensified with glucose lowering drugs or that reached the HbA_{1c} target level (≤53 mmol/mol)	61.1	618/ 1,012	3.8
3.[†] The percentage of patients with T2D between 18 and 70 years treated with two or more non-insulin glucose lowering drugs and with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that started with insulin or that reached the HbA_{1c} target level (≤53 mmol/mol)	38.8	446/ 1,150	4.4
4.[‡] The percentage of patients with T2D 18 years or older that started with metformin among all starters of oral glucose lowering drugs	78.7	841/ 1,069	4.1
5.[‡] The percentage of patients with T2D 18 years or older treated with glucose lowering drugs that is prescribed metformin	86.3	14,984/ 17,353	65.9
6.[‡] The percentage of patients with T2D 18 years or older treated with two non-insulin glucose lowering drugs that is prescribed a combination of metformin and an SU-derivative	87.0	4,865/ 5,589	21.2
7.[‡] The percentage of patients with T2D 18 years or older that started with gliclazide among all starters of an SU-derivative	67.5	666/ 986	3.7
Lipid lowering drugs			
8.[§] The percentage of patients with T2D between 55 and 80 years that is prescribed a statin	71.7	13,123/ 18,301	69.5
9.[†] The percentage of patients with T2D between 18 and 80 years with an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that started with a statin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)	32.1	1,100/ 3,429	13.0

		ZODIAC				
N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison	Outcome score(%)	Nominator/ denominator	Percentage of eligible patients	N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison
76	8,353	80.9	178/ 220	0.4	60	15,323
92	2,376	66.1	846/ 1,280	2.3	87	3,821
92	2,088	42.9	687/ 1,603	2.8	95	3,335
65	1,688	88.4	8,299/ 9,383	16.5	40	238
46	69	88.1	30,360/ 34,451	60.6	41	67
44	205	90.8	10,686/ 11,769	20.7	33	155
85	2,249	18.8	835/ 4,431	7.8	59	754
78	113	76.1	24,428/ 32,079	56.5	70	124
84	643	33.1	1,436/ 4,342	7.6	86	1,113

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Table 5.2: Operational feasibility in GIANTT and ZODIAC database (continued)

	GIANTT		
Indicator	**Outcome score(%)**	**Nominator/ denominator**	**Percentage of eligible patients**
10.† The percentage of patients with T2D between 18 and 80 years treated with simvastatin and with an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that switched to atorvastatin or rosuvastatin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)	46.3	1,105/ 2,389	9.1
Blood pressure lowering drugs			
11.† The percentage of patients with T2D between 18 and 70 years with an elevated systolic blood pressure (>140 mmHg) in the previous year, that started with antihypertensives or that reached the systolic blood pressure target level (≤140 mmHg)	56.9	562/ 988	3.8
12.† The percentage of patients with T2D between 18 and 70 years treated with monotherapy antihypertensives and with an elevated systolic blood pressure (>140 mmHg) in the previous year, that is intensified with antihypertensives or that reached the systolic blood pressure target level (≤140 mmHg)	55.3	588/ 1,064	4.0
Albuminuria lowering drugs			
13.‡ The percentage of patients with T2D 18 years or older treated with two or more antihypertensives that is prescribed an ACE-i or ARB	87.4	12,789/ 14,627	55.6
14.† The percentage of patients with T2D between 18 and 70 years with micro- or macro-albuminuria¶ in the previous year, that started with an ACE-i or ARB or that returned to normo-albuminuria¶	59.5	132/ 222	0.8
15.‡ The percentage of patients with T2D 18 years or older treated with antihypertensives and with micro- or macro-albuminuria¶ that is prescribed an ACE-i or ARB	84.5	2,451/ 2,901	11.0
16.‡ The percentage of patients with T2D 18 years or older that started with an ACE-i among all patients that started with RAAS treatment	70.5	920/ 1,305	5.0
Medication safety			
17. The percentage of patients with T2D 18 years or older treated with SU-derivatives that is prescribed glibenclamide	2.1	163/ 7,859	29.9
18. The percentage of patients with T2D 18 years or older with an eGFR <30 ml/min/1.73m^2 that is prescribed metformin	24.8	91/ 367	1.4

		ZODIAC				
N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison	Outcome score(%)	Nominator/ denominator	Percentage of eligible patients	N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison
96	1,053	45.5	1,587/ 3,488	6.1	96	1,552
95	2,511	63.4	724/ 1,142	2.0	90	4,435
95	2,350	57.1	816/ 1,428	2.5	95	3,743
43	77	84.6	19,381/ 22,902	40.3	51	125
93	10,980	61.0	326/ 534	0.9	92	9,719
51	457	82.6	5,517/ 6,676	11.8	56	470
80	1,612	65.3	5,057/ 7,742	13.6	88	639
781[||]	2,614	3.2	487/ 15,299	26.9	1,190[#]	4,397
287[¶]	20,551	37.2	196/ 527	0.9	359[††]	38,694

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Table 5.2: Operational feasibility in GIANTT and ZODIAC database (continued)

	GIANTT		
Indicator	**Outcome score(%)**	**Nominator/ denominator**	**Percentage of eligible patients**
19. The percentage of patients with T2D 80 years or older with a normal HbA_{1c} level (<53 mmol/mol) that is prescribed two or more glucose lowering drugs	18.2	377/ 2,070	7.9
20. The percentage of patients with T2D 18 years or older treated with RAAS inhibitors that is prescribed a combination of an ACE-i and ARB (dual RAAS blockade)	3.2	502/ 15,714	59.7

GIANTT: Groningen Initiative to Analyse Type 2 diabetes Treatment; ZODIAC: Zwolle Outpatient Diabetes project Integrating Care Study; T2D: type 2 diabetes; HbA1c: glycated haemoglobin; SU-derivative: sulphonylurea derivative; LDL-cholesterol: low-density lipoprotein-cholesterol; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; RAAS: renin-angiotensin-aldosterone system; eGFR: estimated glomerular filtration rate. † Clinical action indicator. ‡ Medication choice indicator. § Current medication use. ¶ Micro- or macro-albuminuria is defined as albumin/creatinine ratio ≥2.5 mg/mmol for males and ≥3.5 mg/mmol for females. Normo-albuminuria is defined as albumin/creatinine ratio <2.5 mmol/l for males and <3.5 mmol/l for females. # Precision of 1 percentage point allowed. †† Precision of 5 percentage point allowed.

included in the previous indicator sets. On the other hand, our PQI set does not include an indicator on the influenza immunization which is included in other sets.[9,11] This indicator was discarded by experts because it could in part reflect behaviour of patients instead of healthcare professionals. The same goes for the indicators focusing on medication adherence.

The PQIs in our set can be divided into indicators that measure the treatment at one point in time, and indicators that make use of sequential data. The latter include the clinical action indicators taking the chronic aspect of diabetes care into account, but also the indicators looking at medication choice when treatment is started. Although such indicators may have a higher face and content validity, the use of additional information can introduce new validity problems. For example, the scores of the PQIs will be influenced by the quality and completeness of data for individual patients in consecutive years. Some PQIs included a low number of patients due to the definitions of patients eligible for starting treatment, where eligible patients could only be identified when the related risk factor measurement from the year before was known. Especially for recently diagnosed patients, such measurements may not be available. Our first sensitivity analysis

		ZODIAC				
N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison	Outcome score(%)	Nominator/ denominator	Percentage of eligible patients	N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison
229[¶]	2,911	21.3	891/ 4,178	7.4	258[††]	3506
1,189[||]	1,991	4.9	1,274/ 26,155	46.0	1,781[#]	3,867

showed that including patients with unknown risk factor measurements in the previous year may lead to higher PQI scores, especially for the PQIs focusing on starting treatment. This could be due to a high prevalence of well-controlled patients among those without a measurement in the previous year or due to a high number of newly diagnosed patients. Also, the misclassification of treatment starters can occur due to a relatively short observation period in the previous year that is used to identify patient who were not yet treated. Our second sensitivity analysis showed that looking at use of treatment at any time point of 12 months in comparison to the last four months, led to including fewer eligible patients and a substantial change in the PQI scores, in particular in the PQIs focusing on start of first-choice drugs. These PQIs do not depend on risk factor measurements, but only include information on drugs use. To reduce misclassification of treatment starts, these indicators could be improved by including an additional requirement that at least one laboratory measurement should be available in the previous year. This indicates that there was a practice visit without a recorded prescription. Finally, several PQIs in our set are restricted to specific cut-off levels of a risk factor as part of the inclusion criteria. This may lead to misclassification of patients that are temporarily well-controlled.[8,31]

PQIs can be used for different purposes, i.e. for monitoring quality of prescribing care, for providing feedback to the healthcare professionals, for research purposes to assess changes over time or after an intervention, and for external benchmarking.[13] However, it is important to be aware that a score of 100% is never pursued. There might be valid reasons why a patient does not receive the recommended treatment, such as an intolerance to a drug or patient's refusal. The PQIs of this set could be used for the first three purposes, but they lack a precision for benchmarking at general practice level.[32] The number of patients with T2D needed per general practice for measuring the quality of prescribing with a precision of 10 percentage point (5 or 1 percentage point for medication safety PQI) ranged from 67 to 38,694. An average general practice in the Netherlands manages around 100 patients with T2D. Furthermore, three PQIs included less than 2% of the total cohort population. When the measured care is applicable to such a small percentage of patients, it can be less appropriate for monitoring purposes. The PQIs including low numbers of patients could instead be more relevant for alerting systems.

Our study has some strengths and limitations. Our initial set was selected using only level A and B evidence recommendations from recent national guidelines, which are similar to international guidelines on most aspects. In some cases, for example, for the indicator on starting statin treatment as a function of LDL-cholesterol, an adaptation might be relevant to incorporate additional risk factors to comply with other guidelines. We confirmed that also topics considered relevant from the patient perspective were included. An expert panel specialised in diabetes care assessed the face and content validity of the PQIs. Judgments made by this panel may not be representative of all diabetes healthcare professionals. However, the number of experts satisfies the requirement to include 7-15 experts to the panel according to the RAM,[24] and it has been argued that using techniques combining evidence with consensus improves the quality of the indicators.[21] We tested the operational validity in different databases, including the ZODIAC database that is representative for the routinely collected data used for monitoring and benchmarking in the Netherlands. Therefore, using this database for testing the operational validity showed that this set of PQIs, including clinical action indicators, can be applied on a national level in Dutch practice. The PQIs can be applied in other settings on the condition that there is a database available that includes information at patient level regarding age, physical examinations, laboratory measurements and prescribed medication. Finally, although our indicators give a good indication of the quality of pharmacotherapy, this cannot be seen as an assessment of overall quality of diabetes care. Other aspects, such as monitoring of patients and outcome parameters might be important as well.

In conclusion, a set of twenty PQIs for patients with T2D was developed and validated, using the RAM method and routinely collected primary care data. This set complements existing T2D quality indicator sets with PQIs that focus on clinical action and medication choice for treatment with glucose lowering, lipid lowering, blood pressure lowering and albuminuria lowering drugs, and medication safety. These PQIs can be used to point out priority areas for improvement and in audit and feedback programs.

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Prescribing quality and prediction of clinical outcomes in patients with type 2 diabetes: a prospective cohort study

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6

Abstract

Background: We assessed whether prescribing quality indicators (PQIs) for type 2 diabetes care are associated with better intermediate outcomes. Special focus was on clinical action indicators measuring start or intensification of treatment when indicated.
Methods: Data were used from the Groningen Initiative to Analyse Type 2 Diabetes Treatment (GIANTT) database, including >26,000 T2D patients. Eleven PQIs measuring prescribing of glucose lowering drugs, statins, antihypertensives, and renin-angiotensin-aldosterone system (RAAS) inhibitors were evaluated. Associations were tested between receiving the recommended treatment in 2012 as measured by each PQI and the related outcome in the following year (glycated haemoglobin, low-density lipoprotein-cholesterol, systolic blood pressure (SBP), albuminuria) using regression models.
Results: Three clinical action PQIs focusing on treatment with glucose lowering drugs were associated with better glycated haemoglobin levels (-5.5 mmol/mol [-9.3,-1.7]; -8.2 mmol/mol [-9.5,-6.9]; -8.8 mmol/mol [-10.1,-7.5]). One current use and two clinical action PQIs on treatment with statins were associated with better low-density lipoprotein-cholesterol levels (-0.29 mmol/l [-0.32,-0.27]; -0.97 mmol/l [-1.04,-0.90]; -0.64 mmol/l [-0.72,-0.56]). Two clinical action PQIs on treatment with antihypertensives were associated with better SBP (-8.63 mmHg [-10.62,-6.63]; -9.95 mmHg [-11.96,-7.95]). The clinical action PQI on treatment with RAAS inhibitors was associated with a lower risk of albuminuria (OR:0.19 [0.08,0.48]). The PQIs on current use of RAAS inhibitors were not associated with a lower risk of albuminuria.
Conclusions: Nine PQIs for type 2 diabetes treatment, including eight clinical action indicators, were associated with better intermediate cardiovascular and renal outcomes, which supports their validity for clinical practice.

Introduction

Guidelines for management of type 2 diabetes (T2D) recommend a stepwise approach to initiate, intensify, and maintain medication treatment in patients with T2D.[1,2] These recommendations are based on evidence from studies on the efficacy and safety of such treatment. It is expected that prescribing as advised in the guidelines will lead to better patient outcomes. Whether patients are treated according to the recommendations can be measured with prescribing quality indicators (PQIs).

PQIs are used for internal and external evaluation of the quality of prescribing. Internal evaluation includes monitoring the quality of care and giving feedback to healthcare professionals, while external evaluation includes benchmarking or pay-for-performance systems.[3] Using indicators in feedback-and-audit programs can lead to better quality of care.[4,5] Nonetheless, when PQIs are, for example, poorly defined or disregard a need for personalized treatment, prescribing according to the PQIs may not be beneficial for all patients.[6] To ensure that the use of PQIs leads to better patient outcomes, their predictive validity needs to be assessed.[7]

There are several types of PQIs.[8] Clinical action indicators measure whether treatment is timely started or intensified.[9] Such action indicators are considered more clinically relevant than the traditional indicators focusing on current medication use.[9-12] Studies showed that several clinical action indicators were predictive of better intermediate patient outcomes.[13-15] Recently, a new set of PQIs for T2D care was developed that included twenty indicators focusing on treatment with glucose lowering drugs, statins, antihypertensives, renin-angiotensin-aldosterone system (RAAS) inhibitors, and medication safety.[16] These PQIs were considered face, content, and operationally valid, but their predictive validity has not yet been assessed. Eleven indicators in this set are expected to have an impact on patient outcomes. Eight of these are clinical action indicators and three focus on current medication use. The aim of this study is to test whether these eleven PQIs are predictive of better intermediate cardiovascular and renal outcomes of patients with T2D.

Methods

A retrospective cohort study was conducted using data from the Groningen Initiative to Analyse Type 2 Diabetes Treatment (GIANTT) database.[17] The GIANTT database contains longitudinal data extracted from medical records of patients with T2D managed in primary care in the north of the Netherlands. The data covers 80% of all general practices in the province of Groningen. All patients that were managed for their T2D in one of the practices for the whole year 2012 were included. The GIANTT database contains all routinely collected data, including information on age, gender, physical examination, laboratory values, comorbidity, and prescribed medication.

The Medical Ethical Committee of University Medical Center Groningen ascertained that the study did not need formal approval with regards to the Medical Research Involving Human Subjects Act, since it used anonymized data from existing databases.

Indicators

The eleven indicators used in this study were defined in the set developed previously (Table 6.1).[16] The eight clinical action indicators focus on start or intensification of treatment with glucose lowering drugs, statins, antihypertensives, and RAAS inhibitors. The three current use indicators focus on prescribing of statins and RAAS inhibitors. Quality of care was assessed in 2012 using these indicators. The clinical action indicators included patients whose last available risk factor value (glycated haemoglobin (HbA_{1c}), low-density lipoprotein(LDL)-cholesterol, systolic blood pressure (SBP), or albuminuria) in 2011 showed insufficient control, and measured the quality of care by looking at whether treatment was initiated or intensified or the risk factor value had returned to control in 2012 (Table 6.1, and Appendix 4, Table S5.2 for PQI definitions). Treatment start and intensification was measured by comparing the medication prescribed in the last four months of 2012 to the last four months of 2011. Current use indicators measured whether the recommended treatment was prescribed in the last four months of 2012 (Figure 6.1). The period of four months was chosen because prescriptions for chronic medication usually have a maximum duration of three months in the Netherlands.

Outcomes

The outcomes were the follow-up values of HbA_{1c}, LDL-cholesterol, SBP, and albuminuria, depending on the PQI (Table 6.1). Albuminuria was dichotomized into normoalbuminuria (albumin/creatinine ratio (ACR) <2.5 mg/mmol for males and <3.5 mg/mmol for females) and micro-/macroalbuminuria (ACR ≥2.5 mg/mmol for males and ≥3.5 mg/mmol for females). Follow-up was defined as the first value in 2013, provided that this was at least thirty days and not more than 365 days after the indicator date. The indicator date was defined as the date of the prescription or the risk factor value that determined the numerator of the PQI in 2012.

Table 6.1: Definition of indicators with the relevant intermediate outcomes and general outcome in a cohort of type 2 diabetes patients in primary care

Indicator	Intermediate patient outcome	Indicator outcome in GIANTT (%, nominator/ denominator)
1. The percentage of patients with T2D between 18 and 70 years with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that started with glucose lowering drugs or that reached the HbA_{1c} target level (≤53 mmol/mol)	Blood glucose	73.1 (174/238)
2. The percentage of patients with T2D between 18 and 70 years on monotherapy metformin and with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that is intensified with glucose lowering drugs or that reached the HbA_{1c} target level (≤53 mmol/mol)	Blood glucose	61.1 (618/1,012)
3. The percentage of patients with T2D between 18 and 70 years with two or more non-insulin glucose lowering drugs and with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that started with insulin or that reached the HbA_{1c} target level (≤53 mmol/mol)	Blood glucose	38.8 (446/1,150)
4. The percentage of patients with T2D between 55 and 80 years that is prescribed a statin	LDL-cholesterol	71.7 (13,123/18,301)
5. The percentage of patients with T2D between 18 and 80 years with an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that started with a statin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)	LDL-cholesterol	32.1 (1,100/3,429)
6. The percentage of patients with T2D between 18 and 80 years treated with simvastatin and with an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that switched to atorvastatin or rosuvastatin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)	LDL-cholesterol	46.3 (1,105/2,389)
7. The percentage of patients with T2D between 18 and 70 years of age with an elevated systolic blood pressure (>140 mmHg) in the previous year, that started with antihypertensives or that reached the systolic blood pressure target level (≤140 mmHg)	Blood pressure	56.9 (562/988)
8.The percentage of patients with T2D between 18 and 70 years treated with monotherapy antihypertensives and with an elevated systolic blood pressure (>140 mmHg) in the previous year, that is intensified with antihypertensives or that reached the systolic blood pressure target level (≤140 mmHg)	Blood pressure	55.3 (588/1,064)
9. The percentage of patients with T2D between 18 and 70 years with micro- or macro-albuminuria† in the previous year, that started with an ACE-i or ARB or that returned to normo-albuminuria†	Albuminuria	59.5 (132/222)
10. The percentage of patients with T2D 18 years or older treated with two or more antihypertensives that is prescribed an ACE-i or ARB	Albuminuria	87.4 (12,789/14,627)

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Table 6.1: Definition of indicators with the relevant intermediate outcomes and general outcome in a cohort of type 2 diabetes patients in primary care (continued)

Indicator	Intermediate patient outcome	Indicator outcome in GIANTT (%, nominator/ denominator)
11. The percentage of patients with T2D 18 years or older treated with antihypertensives and with micro- or macro-albuminuria† that is prescribed an ACE-i or ARB	Albuminuria	84.5 (2,451/2,901)

GIANTT: Groningen Initiative to Analyse Type 2 diabetes Treatment; T2D: type 2 diabetes; HbA_{1c}: glycated haemoglobin; LDL-cholesterol: low-density lipoprotein-cholesterol; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker.
† Micro-/macro-albuminuria is defined as albumin/creatinine ratio ≥2.5 mmol/l for males and ≥3.5 mmol/l for females. Normo-albuminuria is defined as albumin/creatinine ratio <2.5 mmol/l for males and <3.5 mmol/l for females.

Patient characteristics

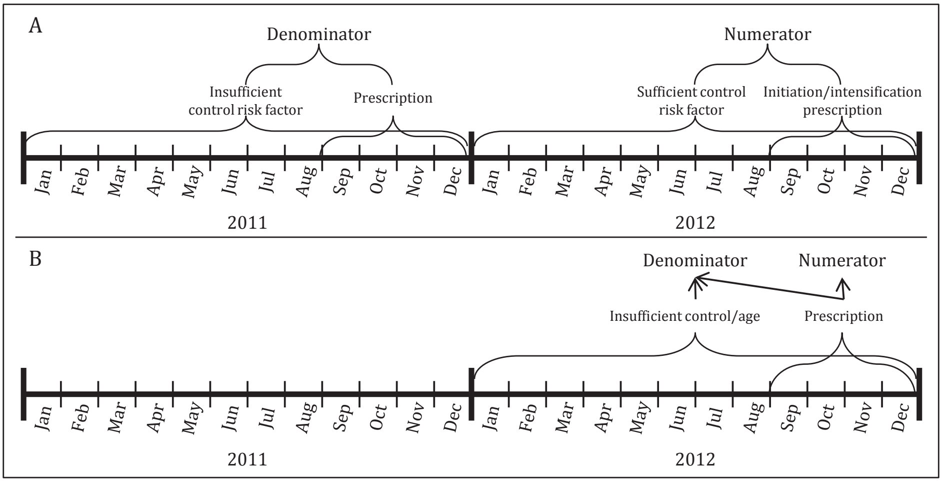
Patient characteristics were included in the models to test whether they would influence the associations between the PQIs and the intermediate patient outcomes. This included age (determined on January 1st, 2012), gender, diabetes duration (categorized on recently diagnosed ≤2 years, less recently diagnosed 2-10 years, and older diagnosed >10 years), baseline risk factor (HbA_{1c}, LDL-cholesterol, SBP, or albuminuria in 2011 for clinical action indicators and in 2012 for current use indicators), time between indicator and outcome date, body mass index (normal <25 kg/m^2, overweight 25-30 kg/m^2, obese ≥30 kg/m^2), and smoking status (yes/no). Furthermore, the following comorbidities were considered: history of cardiovascular disease, peripheral vascular disease, renal complications, diabetic complications, malignancies, and psychological comorbidities (Appendix 5, Table S6.1).

Statistical analysis

Descriptive statistics were used to describe the population in 2012. To test whether the PQIs are predictive of better outcomes, the associations between the indicators and patient outcomes were assessed using linear regression for the continuous outcomes (HbA_{1c}, LDL-cholesterol, SBP values) and logistic regression for the dichotomous outcome (albuminuria).

For each PQI, three separate models were defined for patients with or without good quality of care as defined by the indicator. Model 1 was the primary model, which was adjusted for baseline HbA_{1c}, LDL-cholesterol, SBP, or albuminuria values, depending on the indicator tested. Model 2 tested whether adjusting for

Figure 6.1: Clinical action and current use indicators



A: figure of clinical action indicator. Patients are selected in the denominator when the last available measurement showed insufficient control of the risk factor and there was either no or a predefined treatment prescribed in the last four months of 2011. Patients are selected in the numerator when the last available measurement showed sufficient control of the risk factor and/or a predefined treatment was prescribed in the last four months of 2012. This is a measurement of the initiation or intensification of treatment. B: figure of current use indicators. Patients are selected in the denominator based on either age determined on 1 Jan 2012, insufficient control in the last available measurement of the risk factor in 2012, or a predefined prescription in the last four months of 2012. Patients are selected in the numerator when a predefined treatment was prescribed in the last four months of 2012.

other patients characteristics changed the associations. We included age in this model, and covariates from the predefined list with a p-value below 0.20 using backward selection. When the association is changed by adjusting for a patient characteristic, this could indicate a shortcoming of the indicator. When this is the case, the indicator needs adaptation to reduce unwanted sensitivity to heterogeneity in the underlying patient population. Possibly older patients are prescribed differently than younger patients and have more difficulty with reaching target values. Therefore, Model 3 tested whether patient's age modified the associations by including an interaction term with age. The effect sizes are presented by the estimated differences in outcomes for linear regression and odds ratios (ORs) for logistic regression. The effect sizes were considered statistically significant when the p-value was below 0.05. All analyses were conducted using Stata version 14.1 Special Edition (Stata Corp., College Station, TX).

Sensitivity analysis

LDL-cholesterol and albuminuria values are less frequently available than HbA_{1c} and SBP values. Therefore, a sensitivity analysis was performed extending the follow-up period for the LDL-cholesterol and albuminuria outcomes, that is, allowing for a period of up to 548 days after the indicator date. Furthermore, time between indicator and outcome date may vary between patients, and could influence the association between the indicator and the outcome.[18] A second sensitivity analysis tested for a possible interaction between the indicator and the time between indicator and outcome date.

Role of the funding source

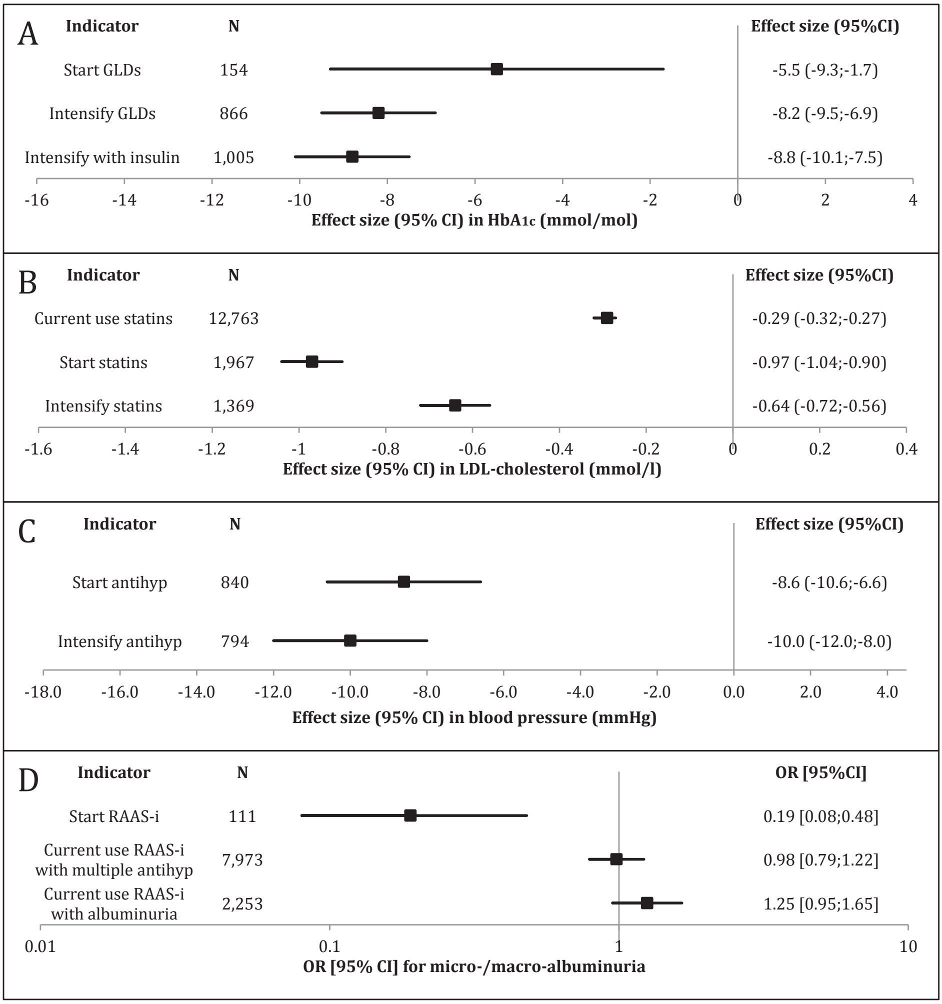
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to the data in the study and had final responsibility for the decision to submit for publication.

Results

In total, 26,321 primary care patients with T2D were included in this study (Table 6.2). At baseline in 2012, they were on average 66.8 years old and 51% was female. The median diabetes duration was 5 years. The percentages of patients with an HbA_{1c}, LDL-cholesterol, SBP, or ACR value were 91%, 81%, 88%, and 69% respectively. Mean HbA_{1c} was 52.0 mmol/mol, mean LDL-cholesterol was 2.61 mmol/l, mean SBP was 140.5 mmHg, and 12% of patients had micro- or macroalbuminuria. Of all patients, 77% were prescribed glucose lowering drugs, 67% were prescribed statins, and 76% were prescribed antihypertensives (Table 6.2).

All three clinical action indicators on start or intensification of treatment with glucose lowering drugs were associated with better HbA_{1c} values at follow-up (Figure 6.2A). Indicator 1 focusing on start of treatment with any glucose lowering drug was associated with an average HbA_{1c} decrease of 5.5 mmol/mol [95%CI -9.3, -1.7]. Indicator 2 focusing on intensification of treatment in patients on metformin monotherapy was associated with an HbA_{1c} decrease of 8.2 mmol/mol [-9.5, -6.9]. Similarly, indicator 3 focusing on initiation of insulin in patients being on multiple non-insulin glucose lowering drugs, was associated with an HbA_{1c} decrease of 8.8 mmol/mol [-10.1, -7.5]. These associations remained similar after adjusting for patient characteristics (effect sizes -5.2 mmol [-9.0, -1.4]; -8.5 mmol [-9.9, -7.2]; -8.9 mmol [10.1, -7.5] respectively, Appendix 5, Table S6.2). The effect

Figure 6.2: Forrest plots showing the effect sizes (A, B, C) and odds ratios (D) for the association between the indicators and the intermediate patient outcomes



95% CI: 95% confidence interval; GLD: glucose lowering drug; HbA_{1c}: glycated haemoglobin; LDL-cholesterol; low-density lipoprotein-cholesterol; antihyp: antihypertensives; RAAS-i: RAAS inhibitors; OR: odds ratios.

A: linear regression associations of the indicators on glucose lowering drugs with HbA_{1c} values in percentages. B: linear regression associations of the indicators on statin use with LDL-cholesterol values. C: linear regression associations of the indicators on antihypertensive treatment with blood pressure values. D: odds ratios of indicators on RAAS inhibitors for risk of having micro- or macro-albuminuria.

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size of indicator 3 was modified by age (p=0.049). Being younger was associated with larger reductions in HbA_{1c} values (Appendix 5, Figure S6.2).

Both the current use indicator and the two clinical action indicators on treatment with statins were associated with better LDL-cholesterol values at follow-up (Figure 6.2B). Indicator 4 focusing on current use of statins was associated with an LDL-cholesterol decrease of 0.29 mmol/l [-0.32, -0.27]. The clinical action indicators 5 and 6 focusing on start and intensification with statins were associated with LDL-cholesterol decreases of 0.97 [-1.04, -0.90] and 0.64 mmol/l [-0.72, -0.56] respectively. These associations remained similar after adjusting for patient characteristics (effect sizes -0.30 [-0.33, -0.27]; -0.97 [-1·03, -0.90]; -0.62 [-0.70, -0.54] respectively, Appendix 5, Table S6.2). There was no significant effect modification by age.

Both clinical action indicators focusing on start and intensification of antihypertensives were associated with better SBP values at follow-up (Figure 6.2C). Indicator 7 focusing on start of treatment was associated with an SBP decrease of 8.63 mmHg [-10.62, -6.63] and indicator 8 on intensification of treatment was associated with an SBP decrease of 9.95 mmHg [-11.96, -7.95]. These associations remained similar after adjusting for patient characteristics (effect sizes -8.38 [-10.36, -6.39] and -9.47 [-11.47, -7.46] respectively, Appendix 5, Table S6.2). There was no significant effect modification of age.

Of the PQIs focusing on treatment with RAAS inhibitors, the clinical action indicator on starting with RAAS inhibitors was significantly associated with the albuminuria values at follow-up (OR: 0.19 [95%CI 0.08, 0.48]). No significant associations were found for indicators 10 and 11 (Figure 6.2D), which focus on current use of RAAS inhibitors (OR: 0.98 [0.79, 1.22]; OR: 1.25 [0.95, 1.65]). These associations remained similar after adjusting for patient characteristics (OR: 0.12 [0.04, 0.34]; OR: 0.94 [0.75, 1.18]; OR: 1.22 [0.92, 1.62] respectively, Appendix 5, Table S6.2). The effect size of indicator 10 was modified by age (p=0.044) but no significant differences were found between the associations according to different age quartiles (Appendix 5, Table S6.3).

The first sensitivity analysis, where the follow-up period was extended to 548 days for the LDL-cholesterol and albuminuria outcomes, did not alter the results (Appendix 5, Figure S6.1). The second sensitivity analysis found one significant effect modification by time between indicator and outcome date. For indicator 6, the association between the indicator and the LDL-cholesterol outcome was stronger for patients with more time between these two dates (Appendix 5, Figure S6.2).

Discussion

Overall, nine out of the eleven PQIs were predictive of better patient outcomes in the following year. All eight clinical action indicators on start and intensification of glucose lowering drugs, statins, antihypertensives, and RAAS inhibitors were predictive of better intermediate cardiovascular and renal outcomes. Of the three current use indicators, only the PQI on current use of statins was predictive of better LDL-cholesterol outcomes. The other two indicators on current use of RAAS inhibitors were not significantly associated with the albuminuria outcome.

Clinical action indicators give more insight for the health care provider than current use indicators.[9,12,19] Previous studies found associations between clinical action indicators and intermediate patient outcomes. A review found evidence that indicators assessing whether glucose and lipid lowering treatment was intensified were predictive of better HbA_{1c} and LDL-cholesterol outcomes.[13] Other studies confirmed these findings.[14,15] While the review did not find an association between intensification of treatment and better SBP outcomes,[13] a more recent study did find such an association.[14] In our study, all clinical action indicators were predictive of better outcomes, including PQIs for various treatment steps to reduce glucose, blood pressure, cholesterol, and albuminuria. The indicators tested in our study differ from most of the previously defined indicators, that is, they also consider patients as receiving adequate treatment when they return to control without a start or intensification of medication treatment. This provides more fair assessment of the quality of care, which may include also interventions on lifestyle, drug dosing, or adherence. In addition, the PQIs we tested were developed using a structured method, providing support for their content and face validity.[7,16] The development process of previously tested indicators was not always clear.[14,15]

PQI focusing on current use of medication are widely used. These are easy to calculate but they do not capture actions of a health care provider in patients who are not sufficiently controlled. Previous studies found mixed results for the predictive validity of these indicators on better intermediate patient outcomes. One study found an association between current use of lipid lowering drugs and better LDL-cholesterol values,[14] which our study confirmed for current use of statins. No associations were found for current use of RAAS inhibitors with albuminuria values,[14] which our study confirmed for patients with or without micro- or macroalbuminuria. Guidelines recommend the use of RAAS inhibitors because of their albuminuria lowering effect.[1,20] Indicators for prescribing of RAAS inhibitors are used in multiple indicator sets for T2D care but also for chronic kidney disease management.[21-23] Their lack of association with patient outcomes suggests that these indicators have no predictive validity. However, this lack of association can also be caused by our use of a dichotomous albuminuria outcome, which is less sensitive to detect changes than a continuous outcome. A continuous variable for albuminuria could not be used due to the presence of values under the detection limit. Since it is not yet certain that patients will benefit from prescribing according to these indicators, they should only be used for internal evaluation to give insight for the health care professionals.

The models were adjusted for the baseline risk factor value, because one can expect that someone with a high baseline risk factor value will have a higher value at the outcome compared to patients with a lower baseline value, despite receiving similar treatment.[24] The models were additionally adjusted for a range of patient characteristics to test for the possible influence of the heterogeneity of the patient population. None of the associations were significantly altered by the adjustments, which was also in line with previous findings for other quality indicators.[18] For one indicator, the association was modified by age but remained significant for all age groups. Therefore none of the tested PQIs needs case-mix adjustment when comparing the quality of care between practices or against a benchmark.

This is a first study testing the predictive validity of clinical action indicators that were developed using a systematic structured approach. We used a database with routinely collected data from a large proportion of patients with T2D cared for in primary care practices to test the predictive validity. The PQIs were tested for associations with intermediate patient outcomes, assuming that this leads to better hard patient outcomes. Previously, however, not all PQIs that were associated with better intermediate outcomes were found to be predictive of better hard patient outcomes.[25] Therefore, additional analyses are needed to test the predictive validity of the PQI on hard patients outcomes.

In conclusion, all eight clinical action PQIs on start and intensification of treatment with glucose lowering drugs, statins, antihypertensives, and RAAS inhibitors and one current use PQI on statins are well defined and beneficial for patients. Therefore these PQIs can be used for internal and external evaluation of the quality of T2D care. Both indicators on current use of RAAS inhibitors do not have sufficient evidence of predictive validity at this point, and should only be used in internal evaluation programs.

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Is guideline-adherent prescribing associated with quality of life in patients with type 2 diabetes?

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Abstract

Background: Guideline-adherent prescribing for treatment of multiple risk factors in type 2 diabetes (T2D) patients is expected to improve clinical outcomes. However, the relationship to Health-Related Quality of Life (HRQoL) is not straightforward since guideline-adherent prescribing can increase medication burden. The aim of study was to test whether guideline-adherent prescribing and disease-specific medication burden are associated with HRQoL in patients with T2D.
Methods: This was a cross-sectional study including 1,044 T2D patients from the e-VitaDM/ZODIAC study in 2012 in the Netherlands. Data from the diabetes visit, such as laboratory and physical examinations and prescribed medication, and from two HRQoL questionnaires, the EuroQol-5D-3L (EQ5D-3L) and the World Health Organization Well-Being Index (WHO-5) were collected. Seven indicators assessing prescribing of renin-angiotensin-aldosterone system (RAAS) inhibitors, statins, and potentially inappropriate drugs from a diabetes indicator set were used. Disease-specific medication burden was assessed using a modified version of the Medication Regimen Complexity Index (MRCI). Associations were tested with regression models, adjusting for age, gender, diabetes duration, comorbidity, BMI and smoking.
Results: The mean MRCI was 7.1, the median EQ5D-3L score was 0.86 and the mean WHO-5 score was 72. Prescribing of RAAS inhibitors and statins was not significantly associated with HRQoL. The indicators assessing inappropriate prescribing included small numbers of patients; prescribing of glibenclamide and dual RAAS blockade was not significantly associated with HRQoL, whereas the indicators assessing inappropriate prescribing of metformin and overprescribing in elderly included too few patients and were excluded from the analysis. Finally, also the MRCI was not associated with HRQoL.
Conclusions: We found no evidence for associations between guideline-adherent prescribing or disease-specific medication burden and HRQoL in T2D patients. This gives no rise to refrain from prescribing intensive treatment in T2D patients as recommended, but the interpretation of these results is limited by the cross-sectional study design and the low number of patients included in some indicators.

Introduction

Clinical guidelines for managing patients with type 2 diabetes (T2D) recommend pharmacotherapy to reduce levels of risk factors such as glycated haemoglobin (HbA_{1c}), blood pressure, low-density lipoprotein (LDL)-cholesterol and albuminuria.[1,2] These recommendations are based on clinical trials assessing the efficacy and safety of these treatments. Patients receiving treatment according to these recommendations show improved intermediate[3] and hard clinical outcomes.[4] It is expected that improved clinical outcomes have a positive effect on health-related quality of life (HRQoL) in patients with T2D.[5] However, following treatment recommendations may also have a negative effect on HRQoL by increasing medication burden and inducing an increased risk for adverse drug events.[6] Medication burden proved to be negatively associated with physical and general HRQoL in various patient populations.[7-9] In addition, prescribing more medication may increase the risk of unsafe or inappropriate prescribing. Previously it was found that the use of inappropriate drugs is associated with reduced general and mental HRQoL in elderly patients.[10] Also, adverse drug events resulting from inappropriate drugs use can negatively influence HRQoL.[8,11]

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Several studies have assessed the association between glucose regulating drugs and HRQoL. These studies found that prescribing of insulin may be associated with lower general but not mental HRQoL[12,13] and prescribing of various oral glucose regulating drugs is not associated with differences in HRQoL.[13,14] Furthermore, one study found that intensive multitherapy for glycaemic, blood pressure and cholesterol control was associated with better general HRQoL compared with usual care.[15] On the other hand, another study found that an increase in the number of glucose, blood pressure and cholesterol regulating drugs did not change HRQoL in T2D patients.[16] Data on the effect of prescribing drug treatment other than glucose regulating drugs or potentially inappropriate drugs in T2D patients on HRQoL is unavailable.

Therefore, the primary aim of this study in T2D patients was to assess the relationship of (I) guideline-adherent prescribing of renin-angiotensin-aldosterone system (RAAS) inhibitors and statins, (II) potentially inappropriate drug prescribing, and (III) disease-specific medication burden with general HRQoL. Secondarily, the relationship with mental HRQoL will be explored.

Methods

A cross-sectional study was conducted using data from the e-VitaDM/ZODIAC study.[17] In short, 1,614 patients with T2D from 69 general practices in the Drenthe region of the Netherlands agreed to participate in a cohort study to investigate the effect of e-health on HRQoL. The database contains routinely collected data from the annual diabetes visit extracted from medical records from these patients. Furthermore, several questionnaires, including the EuroQoL 5 dimensions with 3 levels (EQ5D-3L) and the World Health Organization Well-Being Index (WHO-5) were filled out by the patients either at the general practice or at home. All patients with complete questionnaires, data registered during the yearly extensive diabetes control, and prescription data available were included in this study. All patients with a diagnosis date after 2012, were excluded from the analysis.

This study was approved by the Medical Ethical Review Committee of Isala, Zwolle, the Netherlands, and was registered under Clinicaltrials.gov number NCT01570140.

Patient characteristics

The e-VitaDM/ZODIAC database includes structured data on age, gender, physical examination, laboratory measurements, diabetes-related complications and prescribed medication. Age and diabetes duration (categorized on recently diagnosed ≤2 years, less recently diagnosed 2-10 years, and older diagnosed >10 years) were calculated using the date from the annual diabetes visit. Gender, body mass index (BMI) and smoking (smoking or non-smoking) were determined at the annual diabetes visit. Medication included glucose, blood pressure, and cholesterol regulating drugs. Comorbidities were grouped under coronary artery disease, including history of angina pectoris, coronary artery bypass grafting, myocardial infarct, percutaneous coronary intervention and heart failure, and cerebrovascular disease, including history of cerebrovascular accident and transient ischemic attack.

The quality of prescribing was assessed using the prescribing quality indicators which were systematically developed and validated in the Netherlands.[18]

Prescribing of recommended drugs

Three indicators assessing the recommended prescribing of RAAS inhibitors and statins were included.[18] The indicators focused on prescribing of angiotensin-converting-enzyme inhibitors (ACE-i) or angiotensin-II-receptor-blockers (ARBs) when multiple antihypertensives are prescribed; prescribing of ACE-i or ARBs when albuminuria is present; and prescribing of statins in patients aged 55 to 80 years (Table 7.1).

Table 7.1: Definition of quality indicators used in this study.

Recommended prescribing	
1.	The percentage of patients with T2D between 55 and 80 years that is prescribed a statin
2.	The percentage of patients with T2D 18 years or older treated with two or more antihypertensives that is prescribed an ACE-i or ARB
3.	The percentage of patients with T2D 18 years or older treated with antihypertensives and with micro- or macro-albuminuria† that is prescribed an ACE-i or ARB
Inappropriate prescribing	
4.	The percentage of patients with T2D 18 years or older treated with SU-derivatives that is prescribed glibenclamide
5.	The percentage of patients with T2D 18 years or older with an eGFR <30 ml/min/1.73m^2 that is prescribed metformin
6.	The percentage of patients with T2D 80 years or older with a normal HbA_{1c} level (<53 mmol/mol) that is prescribed two or more glucose regulating drugs
7.	The percentage of patients with T2D 18 years or older treated with RAAS inhibitors that is prescribed a combination of an ACE-i and ARB (dual RAAS blockade)

T2D: type 2 diabetes; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; SU-derivatives: sulfonylurea derivatives; eGFR: estimated glomerular filtration rate; HbA_{1c}: glycated haemoglobin; RAAS: renin-angiotensin-aldosterone system.
† Micro-albuminuria is defined as albumin/creatinine ratio ≥2.5 mg/mmol and <25 mg/mmol for males, ≥3.5 mg/mmol and <35 mg/mmol for females. Macro-albuminuria is defined as albumin/creatinine ratio ≥25 mg/mmol for males, ≥35 mg/mmol for females.

Prescribing of potentially inappropriate drugs

Four indicators assessing the prescribing of potentially inappropriate drugs were included.[18] They focused on prescribing of the non-recommended glibenclamide among sulfonylurea derivative users, prescribing of the contra-indicated metformin among patients with an impaired renal function (eGFR <30 ml/min/1.73m^2), potential overprescribing of glucose regulating drugs in elderly (≥80 years) with low HbA_{1c} values (HbA_{1c} <53 mmol/mol), and prescribing of potentially unsafe dual RAAS blockade (Table 7.1).

Disease-specific medication burden

To assess disease-specific medication burden, we calculated the burden of taking glucose, blood pressure, and cholesterol regulating drugs using a modified version of the Medication Regimen Complexity Index (MRCI).[19] The MRCI comprises of three sections, which are giving burden scores for administration modality, dosing frequency and additional directions. For administration modality, the scores 1 and 4 were used for tablets and injections respectively. For dosing frequency, a score of 1 was used for drugs prescribed once daily, a score of 2 for drugs prescribed twice daily and so on. Furthermore, different scores are used for additional instructions for use. In our dataset, however, data on additional instructions (such as take with a specific fluid or at a specified time) was incomplete. Therefore we used a modified MRCI score, as has been proposed previously.[20] Data on the number of pills prescribed per time was complete and used in the analysis. A score of 1 was used for drugs which had multiple units per time or half a unit per time. Each prescribed drug received an overall score by adding the scores in the sections.

Health-related quality of life

The primary outcome of this study was general HRQoL, assessed by the EQ5D-3L.[21] The EQ5D-3L consists of five questions regarding five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For each question three answer categories are possible; no problems, some problems or extreme problems. This questionnaire has been validated for the Dutch population.[22] The outcome scores range from -0.333 to 1.0, where 1.0 represents perfect HRQoL. The secondary outcome of this study was mental HRQoL, assessed by the WHO-5.[23] The WHO-5 consists of five questions regarding positive mood, vitality and general interest. For each question six answer categories are possible, ranging from constant to never. The WHO-5 score ranges from 0 to 100.

Statistical analysis

Means with standard deviations are reported for normally distributed variables, medians with the inter-quartile range for non-normally distributed variables and percentages for categorical variables. Regression analysis was used to test for associations between the indicators of guideline-adherent prescribing and the HRQoL measures. The residuals of the EQ5D-3L outcome were not normally distributed and therefore did not meet the assumption for linear regression. Since transformation of the variable did not improve the normality, we dichotomized this variable on the median EQ5D-3L score and logistic regression was performed. The WHO-5 scores did satisfy the assumptions for performing linear regression. Two different models were assessed. Model 1 was a crude model and model 2 tested whether the effects sized of the associations were changed by possible confounders. The included confounders were age, gender, diabetes duration, BMI, smoking status and history of coronary artery disease and cerebrovascular disease. Regression models for indicators including less than 50 patients were not assessed, considering the low power, in particular for the adjusted models. P-values below 0.05 were considered statistically significant. All analyses were conducted using Stata version 14.2 Special Edition (Stata Corp., College Station, TX).

Sensitivity analysis

A sensitivity analysis was performed where groups for HRQoL based on the EQ5D-3L were determined on a perfect score (=1) compared to suboptimal score (<1).

Results

Of the 1,614 patients that agreed to participate in the study, patients were excluded from the analysis because they did not have complete data on both the EQ5D-3L and WHO-5 questionnaires (n=423), there was no data available of the annual diabetes control visit (n=125), and when there was no prescription data available (n=22), leaving 1,044 primary care patients with T2D in this study. Of these, 1,035 completed the EQ5D-3L, and 1,011 the WHO-5 questionnaire. The patients were on average 65 years old, 44% was female and the median diabetes duration was 6 years. The mean HbA_{1c} was 50 mmol/mol, the average systolic blood pressure was 136 mmHg, the average LDL-cholesterol 2.4 mmol/l and the median albumin-creatinine ratio (ACR) was 0.7 mg/mmol. Furthermore, 82% of the patients were prescribed glucose regulating drugs, 75% blood pressure regulating drugs, and 78% statins. The score on the MRCI for these three therapeutic classes was on average 7.1 (standard deviation (SD): 4.1) (Table 7.2). The outcome of the indicators for current use ranged from 79% to 86%, while the indicators on inappropriate prescribing ranged from 0% to 15% (Figure 7.1). The indicators focusing on prescribing of metformin with impaired renal function and overprescribing of glucose regulating drugs in the elderly included 1 and 41 patients respectively, and were therefore excluded from the further analysis.

EQ5D-3L

The median score of the total population on the EQ5D-3L questionnaire was 0.86 (interquartile range: 0.81-1.00) (Table 7.2). None of the indicators on recommended prescribing of statins or ACE-i/ARBs, or the indicators on inappropriate prescribing were significantly associated with EQ5D-3L scores in the logistic regression. Higher MRCI scores were significantly associated with lower EQ5D-3L scores. However, after adjustment for age, gender, diabetes duration, BMI and history of coronary disease this association lost significance (Figure 7.2). The sensitivity analysis using a perfect EQ5D-3L score versus all other scores showed similar results (data not shown).

Table 7.2: Baseline characteristics of the study population

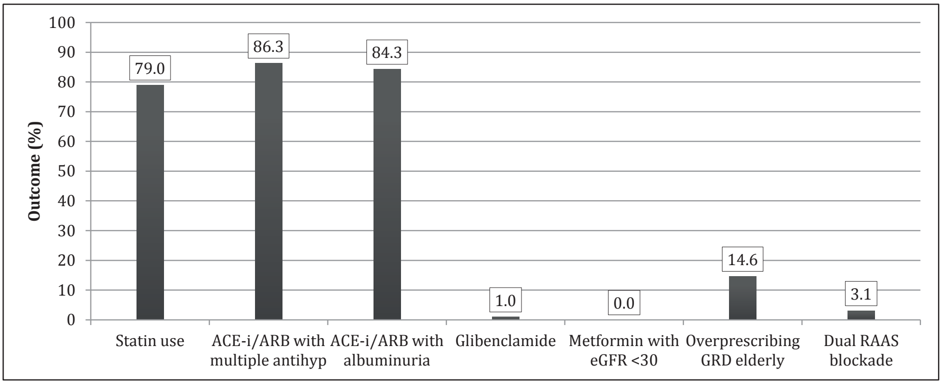
Patient characteristics	N (%)	Mean (±SD)
Patient characteristics		
Age (years)	1,044 (100)	65.2 (±9.8)
≤55 years	152 (14.6)	49.0 (±5.2)
55-80 years	827 (79.2)	66.7 (±6.4)
>80 years	65 (6.2)	83.4 (±2.6)
Female gender	458 (43.9)	
Diabetes duration (years)	1,036 (99.2)	6 [3; 10][a]
≤2 years	254 (24.5)	1.0 (±0.8)
2-10 years	586 (56.6)	6.4 (±2.3)
>10 years (incl. missing values)	196 (18.9)	14.5 (±4.9)
Smoking 2012 (yes)	156 (14.9)	
Physical examination		
Systolic blood pressure 2012 (mmHg)	1,037 (99.3)	135.9 (±15.2)
BMI (kg/m^2)	1,031 (98.8)	29.9 (±5.0)
Normal weight (≤25 kg/m^2)	136 (13.0)	23.5 (±1.2)
Overweight (25-30 kg/m^2)	464 (44.4)	27.5 (±1.4)
Obese (>30 kg/m^2)	431 (41.3)	34.4 (±4.3)
Laboratory measurements		
HbA_{1c} 2012 (mmol/mol)	1,037 (99.3)	49.6 (±8.3)
LDL-cholesterol 2012 (mmol/l)	1,015 (97.2)	2.4 (±0.8)
ACR 2012 (mg/mmol)	945 (90.5)	0.7 [0.3-1.5][a]
eGFR 2012 (ml/min/1.73m^2)	1,036 (99.2)	80.8 (±12.1)
Poor kidney function (<30 ml/min/1.73m^2)	1 (0.1)	28.7 (-)
Medication		
Glucose regulating drugs	853 (81.7)	
Metformin	785 (75.2)	
SU-derivatives	311 (29.8)	
Glibenclamide	3 (0.3)	
Insulin	141 (13.5)	
Blood pressure regulating drugs	782 (74.9)	
Diuretics	346 (33.1)	
Beta blocking agents	426 (40.8)	
Calcium channel blockers	179 (17.2)	
RAAS inhibitors	587 (56.2)	
Statins	811 (77.7)	
Medication Regimen Complexity Index	1,044 (100)	7.1 (±4.1)
Comorbidities		
CAD	203 (19.4)	
CBVD	71 (6.8)	

Table 7.2: Baseline characteristics of the study population (continued)

Patient characteristics	N (%)	Mean (±SD)
HRQoL questionnaires		
EQ5D-3L	1,035 (99.1)	0.86 [0.81-1.00][a]
WHO-5	1,011 (96.8)	71.9 (±17.8)

SD: standard deviation; BMI: body mass index; HbA_{1c}: glycated haemoglobin; LDL-cholesterol: low-density lipoprotein-cholesterol; ACR: albumin/creatinine ratio; eGFR: estimated glomerular filtration rate; SU-derivatives: sulfonylurea derivatives; RAAS: renin-angiotensin-system; CAD: coronary artery disease; CBVD: cerebrovascular disease; HRQoL: health-related quality of life; EQ5D-3L: Euroqol 5 dimensions questionnaire with 3 levels; WHO-5: World Health Organization Well-Being Index.
[a] Median with inter quartile range

Figure 7.1: Outcome of quality indicators in this population in percentages.

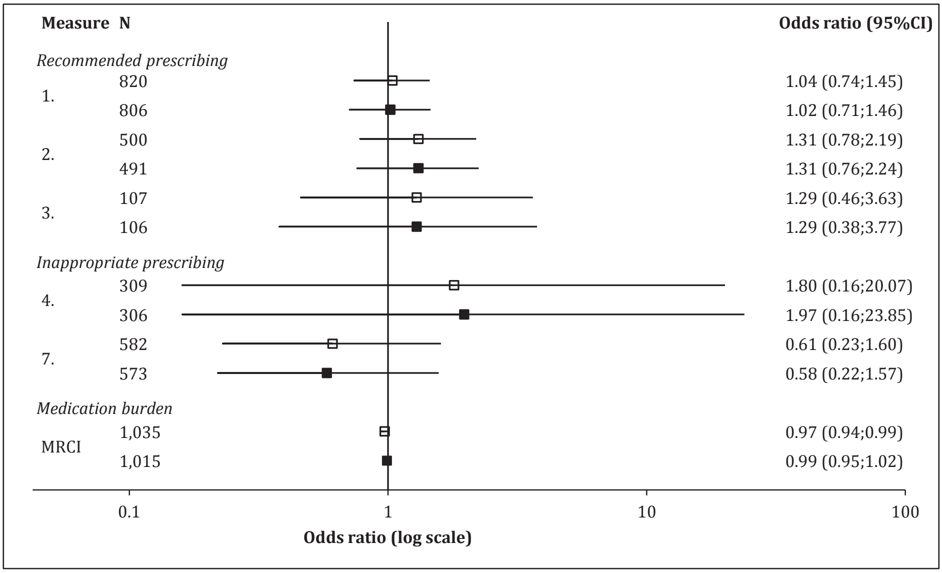


ACE-i: angiotensin-converting-enzyme inhibitors; ARBs: angiotensin-II-receptor-blockers; antihyp: antihypertensives; eGFR: estimated glomerular filtration rate; GRD: glucose regulating drugs; RAAS: renin-angiotensin-aldosterone system.

WHO-5

The mean score on the WHO-5 questionnaire of the total population was 72 (SD: 17) (Table 7.2). None of the indicators on recommended prescribing of RAAS-inhibitors or statins, or the indicators on inappropriate prescribing were significantly associated with higher or lower WHO-5 scores in linear regression. The MRCI for the glucose, blood pressure, and cholesterol regulating drugs was also not associated with WHO-5 scores. Adjustments did not alter the results (Figure 7.3).

Figure 7.2: Overview of odds ratios of guideline-adherent prescribing quality indicators and medication burden with EQ5D-3L scores



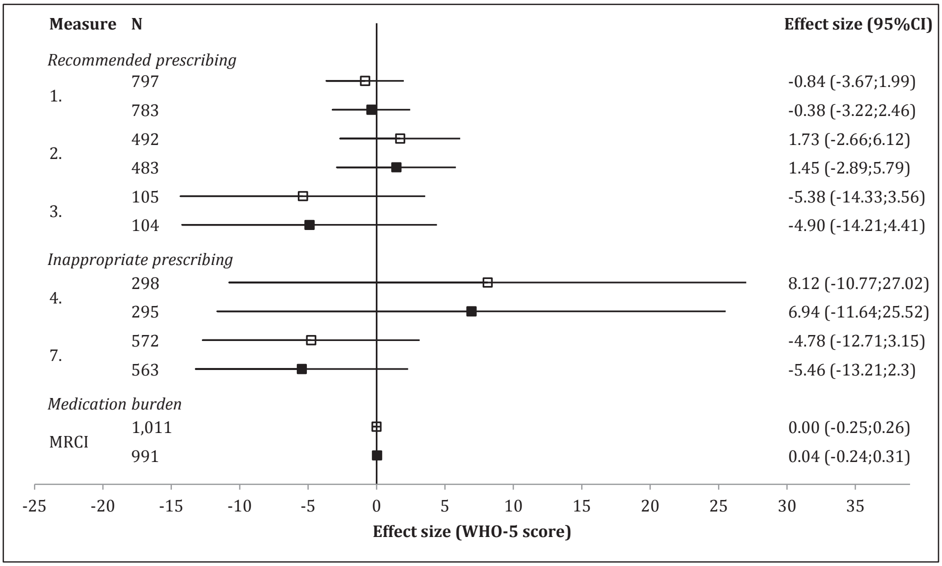
□ represents unadjusted odds ratios; ■ represents adjusted odds ratios; indicator 1: statin prescribing among patients 55-80 years of age; indicator 2: angiotensin-converting-enzyme-inhibitor/angiotensin-II-receptor-blockers prescribing among patients with multiple antihypertensive treatment; indicator 3: angiotensin-converting-enzyme-inhibitor/ angiotensin-II-receptor-blockers prescribing among patients with albuminuria; indicator 4: glibenclamide prescribing among patients with sulfonylurea derivate treatment; indicator 7: dual renin-angiotensin-aldosterone system blockade among patients with renin-angiotensin-aldosterone system-inhibitor treatment; MRCI: medication regimen complexity index.

Discussion

We found no evidence for an association between guideline-adherent prescribing of RAAS-inhibitors or statins and either general or mental HRQoL in T2D patients. Also prescribing of potentially inappropriate medication and having a higher disease-specific medication burden were not associated with HRQoL in patients with T2D.

Our study supports previous findings that prescribing more cardio-protective medication, as recommended by the guidelines, does not influence general or mental HRQoL.[16] This is in contrast to another study, where the association was observed between intensive multitherapy for cardiometabolic risk factors and better general HRQoL.[15] This multitherapy, however, included education and support for improving lifestyle, monthly visits and extensive blood glucose monitoring in addition to medication treatment. Therefore, it is unclear whether the medication

Figure 7.3: Overview of effect sizes of guideline-adherent prescribing quality indicators and medication burden with WHO-5 scores



□ represents unadjusted effect sizes; ■ represents adjusted effect sizes; indicator 1: statin prescribing among patients 55-80 years of age; indicator 2: angiotensin-converting-enzyme-inhibitor/angiotensin-II-receptor-blockers prescribing among patients with multiple antihypertensive treatment; indicator 3: angiotensin-converting-enzyme-inhibitor/ angiotensin-II-receptor-blockers prescribing among patients with albuminuria; indicator 4: glibenclamide prescribing among patients with sulfonylurea derivate treatment; indicator 7: dual renin-angiotensin-aldosterone system blockade among patients with renin-angiotensin-aldosterone system-inhibitor treatment; MRCI: medication regimen complexity index.

treatment in itself influenced the HRQoL. Our findings suggest this may not be the case. The improved lifestyle and diabetes control might be responsible for the improved HRQoL, which has been shown before.[24-27]

The prescribing of potentially inappropriate drugs in elderly patients has found to be associated with reduced general and mental HRQoL.[10] Such findings can be confounded by indication, that is, people who are prescribed more drugs, including potentially inappropriate drugs, may have a poorer health status, which in turn is associated with poorer HRQoL. Our study looked at the prescribing of specific inappropriate drugs in T2D patients, including glibenclamide and dual RAAS blockade. Our findings suggest that general or mental HRQoL is not affected by prescribing of such medication. Possibly, the patients receiving these potentially inappropriate drugs do not perceive any harm at that moment and therefore it did not affect their HRQoL. On the other hand, in this population, only three out of 311 eligible patients were prescribed glibenclamide, and only 18 out of 587 eligible patients were prescribed dual RAAS blockade, which limited the power for these two analyses.

Surprisingly, we also did not find a significant association between the MRCI for glucose, blood pressure, and cholesterol regulating drugs and general or mental HRQoL. Previously, a negative association was found between the overall MRCI and HRQoL in relatively young medication users.[9] Our finding suggests that in patients with a chronic disease, such as T2D, the disease-specific medication burden does not have a significant impact on their HRQoL.

We found no associations between guideline-adherent prescribing and HRQoL, at least when assessed with the EQ5D-3L and WHO-5. Previous research also used other questionnaires, such as the 36-item Short Form Survey. This makes it difficult to compare the results between studies and may explain the inconsistent results found previously. The EQ5D-3L is a widely used and accepted method to assess general HRQoL, and previously differences between treatments have been detected using the EQ5D-3L.[12,28] The T2D patients in this study were relatively well controlled, which might influence the generalizability. On the other hand, the HRQoL was comparable to other T2D populations.[14,16]

This is a first study testing the association between quality indicators of guideline-adherent prescribing and HRQoL in T2D patients. These indicators are part of a larger indicator set to assess quality of prescribing care in T2D, which has previously been validated for content, feasibility, and associations with intermediate outcomes.[18] The analyses were adjusted for several possible confounders. Due to the cross-sectional design of the study, however, it is not possible to assess cause-effect relationships between prescribing and HRQoL. A large proportion of the patients had a high EQ5D-3L score, which we therefore categorized. The categorization may have reduced the power needed to detect significant effects. Furthermore, because of a small number of patients included in two indicators for prescribing of inappropriate drugs, these were excluded from the analyses.

In conclusion, we found no evidence that guideline-adherent prescribing and disease-specific medication burden are related to HRQoL in relatively well-controlled T2D patients. This gives no reason to refrain from prescribing guideline-recommended treatment in T2D patients, at least from a HRQoL perspective, but the interpretation of these results is limited by the cross-sectional study design and the low number of patients included in some indicators.

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General discussion and conclusion

8

Chronic kidney disease (CKD) and type 2 diabetes (T2D) are conditions with a potentially high burden of disease. The impact of both conditions worldwide, in terms of prevalence, suffering of patients, and costs for society is substantial.[1-5] These conditions also carry a high burden of treatment. Pharmacotherapy with proven long-term favourable effects is a major pillar of chronic disease management in these conditions. It can ameliorate the burden of disease by preventing or delaying complications, in case of CKD macrovascular complications, in case of T2D both microvascular and macrovascular complications.[6,7] Preventing or delaying complications contribute to maintaining or even improving quality of life on the longer term.[8] Discussion remains with regards to the short-term effects of specific medication and the extent of the effect of total medication burden on quality of life.

Pharmacotherapy in these conditions is complex, and comprises control of multiple intermediate targets, including blood pressure, dyslipidaemia, in CKD patients the management of proteinuria, anaemia, and electrolyte imbalances, and in T2D glycaemic control.[9-12] To achieve the overall treatment aims of risk reduction and better quality of life in an individual, quality of prescribing should be optimal and preferably personalized, albeit based on broad assumptions with regards to beneficial therapies. Strategies to monitor and, where required, improve prescribing quality will be useful and sometimes imperative to improve overall outcomes in patients.[13]

One way of assessing the prescribing quality in quality improvement initiatives is by the use of prescribing quality indicators (PQIs). PQIs assess whether patients are prescribed the recommended medication according to the guidelines (appropriate prescribing) and do not receive medication that is not needed or potentially unsafe (inappropriate prescribing). In this way, PQIs give insight in the prescribing behaviour of healthcare providers.[14] PQIs need proper development and validation before they can be used to assess the quality of prescribing.[15] When proper actions are taken with regards to the findings of the PQIs, they can contribute to an improved quality of prescribing.[13]

This thesis focuses on the development and validation of two sets of PQIs: one for CKD and one for T2D care. Implementation of these sets in practice will facilitate further steps towards better assessment and improvement of treatment quality.

The set for CKD care comprises sixteen PQIs which showed to have content and face validity. All showed operational validity in primary care, although with some PQIs information was available of only a small number of patients. After excluding two indicators with too few eligible patients, ten out of fourteen PQIs showed operational validity in secondary care. The remaining four indicator required differentiation in albuminuria which was not possible with the extracted data.

The set for T2D care comprises twenty PQIs, including eight clinical action indicators, which showed to have content, face and operational validity in primary care. On top of that, all clinical action indicators and one of the three tested PQIs on current use showed predictive validity when tested for associations with intermediate patient outcomes. No associations were found between the three PQIs on current use and four PQIs on medication safety with improved or lower quality of life.

Strengths of the newly developed sets of prescribing quality indicators

Our newly developed sets of PQIs have several strengths over previously developed quality indicators for CKD and T2D. First of all, although this may sound obvious, a strong point of our sets is that they focus on prescribing, which is a process of care. Processes are easier to change and improve compared to, for example, structure or outcomes of care, which can also be assessed with quality indicators. The prescribing process is a direct action of the healthcare provider, which is relevant to monitor in quality improvement initiatives.

Secondly, previously developed and used PQIs are mainly volume-based indicators, such as the indicators from the Dutch Monitor Prescribing Behaviour General Practitioners.[16] Volume-based indicators focus on prescriptions of certain drugs or drug classes among the whole patient population or prescriptions of preferred drugs among a class of drugs. They are mainly drug- and disease-oriented indicators. These indicators do not necessarily reflect quality of prescribing. The new PQIs described in this thesis include per indicator only eligible patients, for whom the treatment is recommended (or not recommended) in the current clinical guidelines, based on available information on patient characteristics. They are patient-oriented indicators and intended to assess the quality of prescribing according to guidelines. Although PQIs assess quality of prescribing at a population level, due to these restricted inclusion of patients, the PQIs take into account the shift towards more individualized care.

Thirdly, our PQI set for T2D includes clinical action indicators. These clinical action indicators are thought to be more informative for healthcare providers than volume-based or cross-sectional indicators.[17] Volume-based or cross-sectional indicators, that calculate the amount of current prescriptions, may stimulate overtreatment. Furthermore, cross-sectional indicators only focus on one point in time, thereby neglecting the longitudinal nature of chronic care which is needed in CKD and T2D patients. Clinical action indicators are also considered more informative than currently used outcome indicators that focus on numbers of T2D patients achieving target levels.[18] Such outcome indicators do not differentiate between patients who receive suboptimal care and those who are difficult to manage.[18,19] So far, clinical action indicators for T2D have mainly been used for research purposes.[20-23] They have not yet been used in quality improvement initiatives to assess and improve the quality of prescribing. This may in part be due to their complex definitions. The newly developed PQIs, including the clinical action indicators, have been developed and defined in such a way that they can be implemented in quality improvement initiatives and used in daily practice.

Finally, our sets of PQIs include several indicators on prescribing of potentially inappropriate medication. There are lists of indicators or criteria focusing on potentially inappropriate prescribing in elderly[24] and CKD[25], but for T2D such indicators were not included in previous indicator sets for routine assessments.[26,27]

Current concerns regarding prescribing quality indicators

More and more quality indicators are being developed and this thesis partly adds to the number of existing quality indicators. The growing amount of indicators has fuelled the current debate around issues with the data availability, data reliability and usefulness of the indicators.

Data availability concerns the effort it takes to measure, note down, extract and assess clinical information needed to be transformed into quality indicators. The sets of PQIs developed in this thesis are tested on whether it is possible to measure them with the data that are routinely collected and available for quality assessment. This is the operational validity and we concluded that the majority of the PQIs in both sets have this validity, although in some cases the number of eligible patients was very small. This means that there is no extra effort needed to collect data for our PQIs. However, there might be extra effort needed to organise or restructure the extracted data to enable the calculation of the PQIs.

Furthermore, the available data need to be reliable in order to ensure that the indicators correctly reflect the quality of prescribing. The registration of the required variables, such as laboratory measurements and prescription data, should be as complete as possible without errors. The more complete the data are, the more the PQIs reflect the actual quality of prescribing. In this thesis we used both data from validated databases, such as the Groningen Initiative to Analyse Type 2 Diabetes Treatment (GIANTT) database, and data directly from clinical practice.

The amount of missingness differed per database and was lower for validated databases. For indicators that need information about, for example, albuminuria, calcium or phosphate levels, missing data lead to the risk of selection bias.

Finally, well developed and validated indicators are useful to give insight in the quality of care and the possibilities for improvements. Our PQIs were developed to give relevant insights into the prescribing behaviour of healthcare providers, which was confirmed by their face validity. First pilots in practice indicate that our PQIs are of interest for the healthcare providers because of the novel approach of assessing prescribing quality. Quality of prescribing was not assessed in this way before in CKD and T2D patients.

Thus, we expect that the information gained from assessing the quality of prescribing with the newly developed PQIs can be used in future quality improvement initiatives to improve the quality of prescribing in CKD and T2D patients.

Prescribing quality indicators in practice

In general, quality indicators can be used for internal and external evaluation. Examples of internal evaluation are audit-and-feedback programs. Our PQIs can be used in such programs to provide feedback to healthcare providers to make them aware of their performance. Such mirroring can be used to compare healthcare providers and give feedback on the individual, organisational, regional or national level.[28] Our PQIs, specifically the clinical action indicators, are very suitable to identify patients with a possible suboptimal treatment at the individual level, but they can also be used at a higher level, for example, by professional organisations.

As stated by the Health Council of the Netherlands (Gezondheidsraad), quality of care should be made visible.[29] This visibility can be established by using quality indicators in external evaluation. In the Netherlands, hospitals are obliged to report information on the quality of care to the National Health Care Institute (Zorginstituut Nederland). The quality of care is assessed through a set of indicators and the outcomes are accessible online.[30] Patients can use the information to make informed choices about care. The Health Care Inspectorate (Inspectie voor de Gezondheidszorg) uses the information to monitor the quality of secondary care. For primary care, there is the annual Dutch Monitor Prescribing Behaviour General Practitioners.[16] This benchmark currently includes 30 indicators making use of routinely available prescription data. General practitioners can get access to compare their own scores with regional or national scores.

Another way of using PQIs in external evaluation is to use them in pay-for-performance systems. An example of such a system is the Quality Outcomes Framework (QOF) in the United Kingdom.[27] In short, this is an initiative using quality indicators to monitor general practitioners and reward them based on their performance. It is shown that the inclusion of CKD and T2D in the QOF has led to higher awareness, better management and improved outcomes in these patients.[31-33] Also, in The Netherlands, health insurance companies have contracts with partners in primary care that incorporate rewarding based on quality indicators. There is, however, a problem with setting the right benchmarks for rewarding. In the QOF, patients can be excluded from the calculation if the indicated treatment is clinically inappropriate. Some propose that when these exceptions are made, the benchmark of these indicators should be set at 100%, i.e. 100% of included patients should receive the recommended care.[34] Although our PQIs specify the patient population to those for whom the treatment is recommended, a score of 100% is usually not possible and in most cases definitely undesirable.

Quality indicators only assess whether recommendations in guidelines are followed in general. In fact, the daily practice of medicine is composed of elements of evidence-based, preference-based and practice-based medicine.[35] In this way, evidence as reflected in the guidelines is combined with the preferences and needs of individual patients, and the experiences and skills of the healthcare provider. Factors, such as the occurrence or fear for side effects of the drug or not responding to the drug, can justify refraining from prescribing the treatment as recommended by guidelines. As mentioned, in the QOF these reasons can be documented to exclude such patients from the indicators. Registration of all possible aspects will lead to more registration burden, which is unwanted for clinical practice. Still, if 100% is not the benchmark, it remains difficult to set the ‘right’ benchmark. We have not assessed the optimal benchmark for our PQIs, and therefore, one should be careful to use absolute and maximal results of these PQIs in benchmarking programs as being the optimal result.

Instead, using the PQIs in peer comparison, taking notice of major confounding factors in the included population, would be a sensible approach. In such comparisons, differences should be seen as reasons for further inspection and not as results that can easily be interpreted as being right or wrong.

Future perspectives

In this thesis several steps are described toward improved assessment of quality of prescribing. However, there are further steps to take toward the optimal assessment of quality of prescribing.

Predictive validity

Several of the PQIs for T2D care have content, face, operational and predictive validity, and are therefore ready for implementation in quality improvement initiatives. The other PQIs for T2D care and the PQIs for CKD care were yet not tested on predictive validity or, in the case of the PQIs on current prescribing of RAAS-inhibitors, showed no predictive validity. Some of the PQIs, such as the indicators on preferred drug use, may not be associated with clinical outcomes, but could be associated with adverse drug events, better quality of life or other outcomes. The predictive validity of the remaining PQIs would ideally be tested in a cohort study of CKD or T2D patients. Possible patient outcomes to be tested for the other PQIs for T2D care should include the intermediate patient outcomes, such as glycated haemoglobin, low-density lipoprotein-cholesterol, blood pressure and albuminuria, but also adverse events, health-related quality of life and other measures assessing patient perspectives. Similarly, the patient outcomes for the PQIs for CKD care could include kidney function, low-density lipoprotein-cholesterol, blood pressure, phosphate levels, adverse events, health-related quality of life and other patient perspectives. Adverse events might also be linked to the PQIs on potential inappropriate prescribing.

Testing for possible associations with hard patient outcomes, such as cardiovascular disease, end-stage renal disease or death, belongs to the possibilities but is not a prerequisite to give the PQIs predictive validity. For many drug treatments, studies have shown that the intermediate patient outcomes are predictive of hard patient outcomes. This scientific evidence resulted in the clinical guideline recommendations used for our PQIs.[10,11] Therefore, when significant associations are found with intermediate outcomes, as for the nine tested PQIs for T2D care, this is sufficient to support the use of these PQIs in daily practice.

Clinical action indicators

Another step is the development of more clinical action indicators. For CKD care such indicators do not yet exist, and for T2D care there are still possibilities for improvement. For example, it may be useful to track available data in order to detect a trend in the risk factor of interest (is it going up or down, or is it steady?), and determine the need for (intensification of) treatment depending on this trend.

This may account for the situation where a healthcare provider does not start with medication when a risk factor level is above target for the first time. Looking at trends might therefore be a better way of assessing the quality of prescribing. Also, clinical action indicators on potentially inappropriate prescribing for both CKD and T2D could be helpful to support initiatives for deprescribing.

Subsequently, using clinical action indicators will ask for some changes in data collection. Data to calculate quality indicators usually only include data from one year. To be able to systematically calculate clinical action indicators, data over multiple consecutive years should be available and linked at individual patient level. Only then the clinical action indicators can be implemented in daily practice.

Updating prescribing quality indicator sets

Quality indicators are derived from evidence-based clinical guidelines. It is important to keep the quality indicators updated and compliant with each new guideline. Although in our sets the most recent guidelines were used, some of the recommendations may be somewhat outdated. In the Netherlands, a new multidisciplinary guideline for CKD care will be issued in the near future. Some of our PQIs will need adaptation to become compliant with this new guideline. The same will hold for the PQIs for T2D care when an update of the guideline will be released. Ideally, each new guideline should be accompanied by a list of valid quality indicators. To take a step towards this ideal situation, the possibility to incorporate (an adapted version of) our set of PQIs for CKD care within primary care with the new guideline is explored together with the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap).

Furthermore, during the development phase of the indicator sets, several PQIs have been discarded. The reasons were diverse but some were discarded because the experts felt it was not possible or necessary to calculate them at that time. This included, for instance, PQIs assessing medication adherence by patients. However, times may change and in the future some of these PQIs might become measurable or important. Also other types of processes of care, such as lifestyle recommendations in addition to medication treatment, may be incorporated in the indicator sets. Therefore, in the future the possibilities should be explored of including appropriate indicators on those fields in indicator sets for T2D care and CKD care.

Clinical decision support and research purposes

Some of the PQIs may be incorporated in clinical decision support systems. Clinical decision support systems aid the healthcare provider to make the right choice of treatment, for instance, depending on risk factor levels or preferred drug choices.[36] Our PQIs focusing on recommended treatments could be translated to algorithms for clinical decision support systems.[37,38] For example, they could make the healthcare provider aware of the preferred choices or possible missed opportunities to improve the quality of prescribing. Furthermore, the indicators focusing on potentially inappropriate prescribing may be incorporated as alerts in existing alert systems.

PQIs can also be used for research purposes to identify areas for improvement and/or factors associated with suboptimal prescribing, as we did for the current quality of CKD care in three outpatient clinics in the Netherlands. PQIs are also used in intervention studies to test whether, for example, giving audit and feedback results in improved prescribing behaviour of the healthcare providers. A Cochrane review showed that there are different ways of providing audit and feedback, and that some appear more effective than others.[13] Therefore, different interventions using the PQIs can be tested. The findings can be used to develop a successful intervention to improve the quality of prescribing. Even looking further ahead, a successful intervention could possibly trigger the development and validation of other sets of PQIs to improve the quality of prescribing among other patient populations.

So, although we are not at the end of the path towards the optimal assessment of the quality of prescribing and improving treatment of patients with CKD and/or T2D, we did take several important steps. This thesis presents two comprehensive, validated and workable sets of PQIs that can be implemented in practice for assessing and improving the quality of prescribing in CKD and in T2D care.

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English summary

Chronic kidney disease (CKD) and type 2 diabetes (T2D) are conditions with a (potentially) high burden of disease worldwide, in terms of prevalence, suffering of individual patients, and costs for society. These conditions also carry a high burden of treatment. Pharmacotherapy is a major pillar of chronic disease management in these conditions to control multiple intermediate targets, including blood pressure, dyslipidaemia, glycaemic control, proteinuria and electrolyte imbalances. To achieve the overall treatment aims of risk reduction and better quality of life of the patient, the quality of prescribing should be optimal. One way of assessing the quality of prescribing is by the use of prescribing quality indicators (PQIs). PQIs assess whether patients are prescribed according to the guidelines and give insight in the prescribing behaviour of healthcare providers. PQIs which are properly developed and validated can be used in assessing the quality of prescribing. This thesis is focused on the development and validation of two sets of PQIs: one for CKD and one for T2D care.

Part I: Quality of prescribing in chronic kidney disease

The aims of the first part of this thesis are to (I) give an overview of existing quality indicators to assess processes of CKD care with a systematic literature review, (II) develop and validate a set of PQIs for CKD care and (III) apply this set to assess the current quality of prescribing in CKD patients.

The review of existing process quality indicators used in research and daily practice showed that many indicators exist already (**Chapter 2**). The indicators found focused on monitoring of kidney function and vascular risk factors, treatment, drug safety, adherence and referral to a specialist. None of these indicators was sufficiently validated on all four assessed validities, i.e. content, face, operational and predictive validity. A few indicators were sufficiently validated on content, face and operational validity. These included some indicators focusing on monitoring of kidney function and vascular risk factors in patients with CKD, and some regarding prescribing focusing on underprescribing of renin-angiotensin-aldosterone system (RAAS) inhibitors and inappropriate use of non-steroidal anti-inflammatory drugs (NSAIDs), nitrofurantoin and bisphosphonates.

In the second project (**Chapter 3**), we describe the process of development steps of a set of sixteen PQIs with an expert panel of general practitioners, nephrologists and pharmacists. This set is intended for assessing the quality of prescribing in both primary and secondary CKD care. The PQIs focus on prescribing of antihypertensives, RAAS inhibitors, statins and phosphate binders when recommended and the potential inappropriate prescribing of dual RAAS blockade, erythropoiesis-stimulating agents (ESA), metformin, active vitamin D and NSAIDs. Some PQIs were discarded during the development phase. These included PQIs focusing on preferred prescribing of RAAS inhibitors among anti-hypertensives (without the presence of albuminuria), start of phosphate binders, underprescribing of vitamin D, iron supplements and ESA, monitoring of potassium when RAAS inhibitors and diuretics are used simultaneously and prescribing of an fixed-combination pill. After the development, the set was tested using the data of primary care patients with T2D and CKD from the Groningen Initiative to Analyse Type 2 diabetes Treatment (GIANTT) database. The results showed that it was feasible to calculate all sixteen PQIs using the available data derived from a primary care database, although for some PQIs information was available of only a small number of patients. After this structured development process and based on these results, we concluded that this set of PQIs for CKD care has content, face and operational validity for primary care (table ES.1).

In a next step, the current quality of prescribing in a secondary care population was assessed by these new PQIs using data from three nephrology outpatient clinic, of which two are academic and one is non-academic (**Chapter 4**). The indicators on non-calcium containing or calcium-containing phosphate binders were not assessed, due to the limited number of included patients. Furthermore, due to limited availability of albumin/creatinine ratios, the indicators focusing on prescribing of RAAS inhibitors in the presence of diabetes and micro-albuminuria were not assessed, and proteinuria was used as a proxy for macro-albuminuria. The results showed low prescribing rates of RAAS inhibitors and statins when recommended, and high prescribing rates of active vitamin D when potentially inappropriate. Besides, several differences were observed between CKD stages. We observed less prescribing of recommended RAAS inhibitors in patients with CKD stage 5. On the other hand, in patients with CKD stage 3 we observed less prescribing of statins, but also less prescribing of potentially inappropriate active vitamin D and ESA. In addition, we also observed several differences between the outpatient clinics, even after stratification for CKD stage. This study showed it was feasible to calculate these PQIs using the available data derived from Hospital Information Systems. Therefore, we can conclude that this adapted set of PQIs also has operational validity in secondary care (table ES.1).

Table ES.1: Developed prescribing quality indicators for chronic kidney disease and their validity

Prescribing quality indicator	Validity: Content	Face	Operational 1st†	Operational 2nd†	Predictive
1. The percentage of patients with CKD stages 4-5 between 18 and 80 years with hypertension‡, that is prescribed antihypertensives unless undesirable because of low diastolic blood pressure (<70 mmHg)	√	√	√	√	0
2a. The percentage of patients with CKD stages 3-5 between 18 and 80 years with macro-albuminuria§ treated with multiple antihypertensives, that is prescribed a combination of an ACE-i or ARB and a diuretic	√	√	√	√¶	0
2b. The percentage of patients with CKD stages 3-5 between 18 and 80 years with micro-albuminuria§ and diabetes# treated with multiple antihypertensives, that is prescribed a combination of an ACE-i or ARB and a diuretic	√	√	√	-	0
3a. The percentage of patients with CKD stages 3-5 between 18 and 80 years with macro-albuminuria§, that is prescribed an ACE-i or ARB	√	√	√	√¶	0
3b. The percentage of patients with CKD stages 3-5 between 18 and 80 years with micro-albuminuria§ and diabetes#, that is prescribed an ACE-i or ARB	√	√	√	-	0
4. The percentage of patients with CKD stages 3-5 between 50 and 65 years, that is prescribed a statin	√	√	√	√	0
5. The percentage of patients with CKD stages 3-5 between 18 and 80 years with an elevated phosphate level (>1.49 mmol/l), that is prescribed a phosphate binder	√	√	√††	√	0
6. The percentage of patients with CKD stages 3-5 between 18 and 80 years treated with phosphate binders and with an elevated calcium level (>2.54 mmol/l), that is prescribed a non-calcium-containing phosphate binder	√	√	√††	0	0
7. The percentage of patients with CKD stages 3-5 between 18 and 80 years treated with phosphate binders and with a low calcium level (<2.10 mmol/l), that is prescribed a calcium-containing phosphate binder	√	√	√††	0	0
8. The percentage of patients with CKD stages 3-5 18 years or older treated with RAAS inhibitors, that is prescribed at least two RAAS inhibitors simultaneously (dual RAAS blockade)	√	√	√	√	0
9. The percentage of patients with CKD stages 3-5 18 years or older with an elevated calcium level (>2.54 mmol/l), that is prescribed active vitamin D	√	√	√††	√	0
10. The percentage of patients with CKD stages 3-5 18 years or older with an haemoglobin level above target (≥7.5 mmol/l), that is prescribed an ESA	√	√	√	√	0

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Table ES.1: Developed prescribing quality indicators for chronic kidney disease and their validity (continued)

Prescribing quality indicator	Validity				
	Content	Face	Operational		Predictive
			1st†	2nd†	
11. The percentage of patients with eGFR <30ml/min/1.73m^2 18 years or older, that is prescribed an NSAID	√	√	√	√	0
12. The percentage of patients with eGFR <30 ml/min/1.73m^2 18 years or older with diabetes#, that is prescribed metformin	√	√	√	√	0
13. The percentage of patients with eGFR <50 ml/min/1.73m^2 18 years or older, that is prescribed high dose digoxin (>0.125 mg/day)	√	√	√	√	0
14. The percentage of patients with CKD stages 3-5 18 years or older, that is prescribed a combination of NSAIDs, RAAS inhibitors and diuretics	√	√	√	√	0

CKD: chronic kidney disease; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; RAAS: renin-angiotensin-aldosterone system; ESA: erythropoiesis-stimulating agent; eGFR: estimated glomerular filtration rate; NSAID: non-steroidal anti-inflammatory drug.
† 1st: primary care, 2nd: secondary care. ‡ Hypertension is defined as having a systolic blood pressure > 140 mmHg or being prescribed antihypertensives. § Micro-albuminuria is defined as albumin/creatinine ratio ≥3.0 mg/mmol and <30 mg/mmol. Macro-albuminuria is defined as albumin/creatinine ratio ≥30 mg/mmol. ¶ These indicators were tested using proteinuria (>0.5 g/l urine) as a proxy for macro-albuminuria, since the albumin/creatinine ratio was only limited available. # Diabetes is defined as either the diagnosis for diabetes or being prescribed with glucose lowering drugs. †† These indicators showed operational validity, but included <2% of the source patient population and are therefore mainly suitable for internal evaluation. Content validity: √ = developed based on guidelines. Face/operational/predictive validity: √ = tested and valid; - = not valid; 0 = not tested.

Part II: Quality of prescribing in type 2 diabetes

The aims of the second part of this thesis are to (I) develop and validate a new set of PQIs for T2D in primary care with a focus on clinical action indicators, (II) test for possible associations between these PQIs and related intermediate patient outcomes and (III) test for possible associations between these PQIs and health-related quality of life in T2D patients.

A set of twenty PQIs for diabetes care was developed with an expert panel of internists and general practitioners (**Chapter 5**). The set includes PQIs focusing on treatment with glucose lowering drugs, antihypertensives, RAAS inhibitors and statins when recommended, and on potential inappropriate prescribing of

Table ES.2: Developed prescribing quality indicators for type 2 diabetes and their validity

Prescribing quality indicator	Validity			
	Content	Face	Operational	Predictive†
1. The percentage of patients with T2D between the ages 18 and 70 years with elevated HbA_{1C} level (>53 mmol/mol) in the previous year that started with glucose lowering drugs or that reached the HbA_{1C} target level (≤53 mmol/mol)	√	√	√‡	√
2. The percentage of patients with T2D between the ages 18 and 70 years on monotherapy metformin and an elevated HbA_{1C} level (>53 mmol/mol) in the previous year, that is intensified or that reached the HbA_{1C} target level (≤53 mmol/mol)	√	√	√	√
3. The percentage of patients with T2D between the ages 18 and 70 years with two or more non-insulin glucose lowering drugs and an elevated HbA_{1C} level (>53 mmol/mol) in the previous year that started with insulin or that reached the HbA_{1C} target level (≤53 mmol/mol)	√	√	√	√
4. The percentage of patients with T2D that started with metformin among all starters of oral glucose lowering drugs	√	√	√	0
5. The percentage of patients with T2D treated with metformin among all patients treated with glucose lowering drugs	√	√	√	0
6. The percentage of patients with T2D treated with metformin and an SU-derivative among all patients treated with two non-insulin glucose lowering drugs	√	√	√	0
7. The percentage of patients with T2D that started with gliclazide among all starters of an SU-derivative	√	√	√	0
8. The percentage of patients with T2D between 55 and 80 years old that is treated with statins	√	√	√	√
9. The percentage of patients with T2D between the ages 18 and 80 years with an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that started with a statin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)	√	√	√	√
10. The percentage of patients with T2D between the ages 18 and 80 years treated with simvastatin and an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that switched to atorvastatin or rosuvastatin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)	√	√	√	√
11. The percentage of patients with T2D between the ages 18 and 70 years of age and an elevated systolic blood pressure (>140 mmHg) in the previous year that started with antihypertensives or reached the systolic blood pressure target level (≤140 mmHg)	√	√	√	√

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Table ES.2: Developed prescribing quality indicators for type 2 diabetes and their validity (continued)

	Validity			
Prescribing quality indicator	**Content**	**Face**	**Operational**	**Predictive**†
12.The percentage of patients with T2D between the ages 18 and 70 years treated with monotherapy antihypertensives and an elevated systolic blood pressure (>140 mmHg) in the previous year, that is treatment was intensified or that reached the systolic blood pressure target level (≤140 mmHg)	√	√	√	√
13. The percentage of patients with T2D and treated with two or more antihypertensives that is treated with an ACE-i or ARB	√	√	√	-
14. The percentage of patients with T2D between the ages 18 and 70 years with micro- or macro-albuminuria§ in the previous year that started with an ACE-i or ARB or that returned to normo-albuminuria§	√	√	√‡	√
15. The percentage of patients with T2D treated with antihypertensives and micro- or macro-albuminuria§ that is treated with an ACE-i or ARB	√	√	√	-
16. The percentage of patients with T2D that started with an ACE-i among all patients that started with RAAS treatment	√	√	√	0
17. The percentage of patients with T2D that is treated with glibenclamide among all patients treated with SU-derivatives	√	√	√	0
18. The percentage of patients with T2D and an eGFR <30 ml/min/1.73m^2 that is treated with metformin	√	√	√‡	0
19. The percentage of patients with T2D 80 years or older and a normal HbA_{1C} level (<53 mmol/mol) that is treated with two or more glucose lowering drugs	√	√	√	0
20. The percentage of patients with T2D that is treated with a combination of an ACE-i and an ARB (dual RAAS blockade) among all patients with RAAS treatment	√	√	√	0

T2D: type 2 diabetes; HbA_{1c}: glycated haemoglobin; SU-derivative: sulphonylurea derivative; LDL-cholesterol: low-density lipoprotein-cholesterol; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; RAAS: renin-angiotensin-aldosterone system; eGFR: estimated glomerular filtration rate.

† Predictive validity with intermediate patient outcomes. ‡ These indicators were operational valid, but included <2% of the source patient population and are therefore mainly suitable for internal evaluation. § Micro-/macro-albuminuria is defined as albumin/creatinine ratio ≥2.5 mmol/l for males and ≥3.5 mmol/l for females. Normo-albuminuria is defined as albumin/creatinine ratio <2.5 mmol/l for males and <3.5 mmol/l for females. Content validity: √ = developed based on guidelines. Face/operational/predictive validity: √ = tested and valid; - = not valid; 0 = not tested.

glibenclamide, metformin, dual RAAS blockade and potential overtreatment with glucose lowering drugs. Eight of the PQIs in the set are clinical action indicators focusing on timely start or intensification of recommended treatment. During the development, several PQIs were discarded. Those excluded were volume-indicators on the use of glucose lowering drugs and PQIs on appropriate prescribing of glucose lowering drugs in elderly T2D patients, preferred use of simvastatin, start of antihypertensives stratified to age and blood pressure level, potential inappropriate prescribing of a combination of pioglitazone and insulin and intensification of antihypertensives in elderly patients, monitoring of potassium when RAAS inhibitors or diuretics are prescribed, flu vaccination and treatment adherence for glucose lowering drugs, lipid lowering drugs and antihypertensives. After development, the set was tested in two databases of patients with T2D from primary care (GIANTT and Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC)). The results showed that all twenty PQIs were feasible to assess the quality of prescribing using the available data, although some PQIs included a small number of patients due to limited availability of data. Following these results and their structured development, we concluded that this set of PQIs for T2D care has content, face and operational validity in primary care (table ES.2).

Thereafter, the associations of several PQIs with intermediate patient outcomes were tested (**Chapter 6**). For this study, eleven PQIs were selected which were assumed to have an influence on levels of glycated haemoglobin (HbA_{1c}), low-density lipoprotein-cholesterol(LDL)-cholesterol, blood pressure or prevalence of albuminuria. The tested PQIs were the eight clinical action indicators, one indicator on current prescribing of statins and two on current prescribing of RAAS inhibitors. The results showed that the clinical action indicators on glucose lowering drugs were significantly associated with lower HbA1c levels one year later. Similarly, both the clinical action indicators and the indicator on current prescription of statins, both clinical action indicators on antihypertensive treatment and the clinical action indicator on RAAS inhibitor treatment showed significant associations with respectively lower LDL-cholesterol levels, lower blood pressure and lower risk of albuminuria. The two indicators on current prescription of RAAS inhibitors were not associated with the risk of albuminuria one year later. Therefore all tested PQIs except for the ones on current prescription of RAAS inhibitor showed predictive validity with intermediate patient outcomes (table ES.2).

Finally, we assessed possible associations of guideline-adherent prescribing and disease-specific medication burden with health-related quality of life (HRQoL) in T2D patients (**Chapter 7**). To assess guideline-adherent prescribing, seven PQIs were selected. This selection was based on the data availability of the patients within the e-Vita/ZODIAC study. For most of them, data of multiple years were unavailable and calculating the clinical action indicators was therefore not feasible. The selected PQIs were three indicators on current prescribing of statins and RAAS inhibitors when recommended and four PQIs on potential inappropriate prescribing of glibenclamide, metformin and dual RAAS blockade and potential overprescribing of glucose lowering drugs in the elderly T2D patients are used. Disease-specific medication burden was assessed using a modified version of the Medication Regimen Complexity Index. The disease-specific medication included glucose lowering drugs, statins and antihypertensives. HRQoL was assessed through both the Euroqol 5 dimensions 3 levels (EQ5D-3L) questionnaire and the World Health Organization Well-Being Index. Both questionnaires are short, including five questions, which gives an indication of the general and mental HRQoL respectively. A large proportion of the patients scored high on the EQ5D-3L and the outcome was therefore dichotomized. Guideline-adherent prescribing assessed by the seven PQIs was not significantly associated with HRQoL in T2D patients. Also, no significant association was found between disease-specific medication burden and HRQoL. The power of detecting an association with HRQoL, however, was limited by low numbers of included patients. Moreover, the dichotomization of the EQ5D-3L may also have reduced the power to detect associations. Therefore, we concluded that at this time, there was no evidence for guideline-adherent prescribing or medication burden influencing the quality of life in T2D patients.

Conclusion

This thesis resulted in two sets of valid PQIs for assessing the quality of prescribing in CKD and T2D care. Several of these PQIs are ready for implementation in quality improvement initiatives, such as audit-and-feedback programs. Some of the PQIs need more testing, especially for predictive validity (table ES.1 and ES.2). Nonetheless, this thesis denotes important steps towards a better assessment of the quality of prescribing and optimal pharmacotherapy in patients with CKD or T2D.

Nederlandse samenvatting

Chronische nierschade (CNS) en type 2 diabetes (T2D) zijn ziekten met een (potentiële) hoge ziektelast wereldwijd in prevalentie, het lijden van individuele patiënten en de kosten voor de maatschappij. Daarnaast hebben deze ziekten ook een hoge behandellast. Farmacotherapie is belangrijk in het management van de ziekten om verschillende risicofactoren onder controle te houden, zoals de bloeddruk, het cholesterol, de bloedglucose, de proteïnurie en het elektrolytenbalans. De kwaliteit van voorschrijven dient optimaal te zijn om de behandeldoelen te halen en de kwaliteit van leven van de patiënten verbeteren. Deze kwaliteit van voorschrijven kan beoordeeld worden door voorschrijfindicatoren. Voorschrijfindicatoren brengen in kaart of patiënten volgens de richtlijnen worden voorgeschreven en geven inzicht in het voorschrijfgedrag van zorgverleners. Voor gebruik in de dagelijkse praktijk en onderzoek, dienen voorschrijfindicatoren goed ontwikkeld en gevalideerd te zijn. Dit proefschrift beschrijft de ontwikkeling en validatie van twee sets van voorschrijfindicatoren: één voor CNS en één voor T2D patiënten.

Deel I: Kwaliteit van voorschrijven bij CNS

De doelstellingen van het eerste deel van dit proefschrift zijn (I) om een overzicht te geven van bestaande procesindicatoren voor CNS met behulp van een systematisch literatuuronderzoek, (II) het ontwikkelen en valideren van een set van voorschrijfindicatoren voor CNS en (III) het toepassen van deze set om de huidige kwaliteit van voorschrijven bij CNS patiënten te beoordelen.

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Het systematisch literatuuronderzoek naar bestaande procesindicatoren liet zien dat er veel kwaliteitsindicatoren bestaan die processen van zorg beoordelen (**Hoofdstuk 2**). De gevonden procesindicatoren beoordelen het monitoren van de nierfunctie en vasculaire risicofactoren, behandeling, medicatieveiligheid, therapietrouw en verwijzing naar de specialist. Geen van deze indicatoren was getest op alle vier de beoordeelde validiteiten, dat wil zeggen de inhouds-, indruks-, operationele en voorspellende validiteit. Enkele indicatoren waren voldoende gevalideerd op inhouds-, indruks- en operationele validiteit. Deze indicatoren richtten zich op het monitoren van nierfunctie en vasculaire risicofactoren bij patiënten met CNS, het voorschrijven van renine-angiotensine-aldosteronsysteem (RAAS) remmers en het ongepaste gebruik van niet-steroïde anti-inflammatoire geneesmiddelen (NSAIDs), nitrofurantoïne en bisfosfonaten.

In het tweede project (**Hoofdstuk 3**) beschrijven we het proces van de ontwikkeling van een set van zestien voorschrijfindicatoren met behulp van een deskundig panel van huisartsen, nefrologen en apothekers. De voorschrijfindicatoren richten zich op het voorschrijven van antihypertensiva, RAAS-remmers, statines en fosfaatbinders zoals aanbevolen in de richtlijnen en het mogelijke ongepaste voorschrijven van dubbele RAAS-blokkade, erytropoëse-stimulerende middelen (ESA), metformine, actieve vitamine D en NSAIDs. Sommige voorschrijfindicatoren zijn verworpen gedurende de ontwikkelingsfase. Zij richtten zich op voorschrijven van RAAS-remmers in aanwezigheid van antihypertensiva (zonder aanwezigheid van albuminurie), start met fosfaatbinders, onderbehandeling van vitamine D, ijzersupplementen en ESA, het monitoren van kalium wanneer RAAS-remmers en diuretica gelijktijdig voorgeschreven worden en het voorschrijven van een vaste combinatiepil. De overgebleven voorschrijfindicatoren zijn getest met behulp van de gegevens van patiënten met T2D en CNS in de eerstelijnszorg uit het Groningen Initiative to Analyse Type 2 diabetes Treatment (GIANTT) database. Uit de resultaten bleek dat alle zestien voorschrijfindicatoren te berekenen zijn door gebruik te maken van de beschikbare gegevens afkomstig uit een eerstelijnszorg database. Voor sommige voorschrijfindicatoren konden echter slechts enkele patiënten worden geïncludeerd. Na het gestructureerde ontwikkelingsproces en op basis van deze resultaten kunnen we concluderen dat deze set van voorschrijfindicatoren voor CNS inhouds-, indruks- en operationeel valide is in de eerstelijnszorg (tabel NS.1).

In een volgende stap werd de huidige kwaliteit van het voorschrijven in een tweedelijnszorg populatie beoordeeld met behulp van deze voorschrijfindicatoren (**Hoofdstuk 4**). Hierbij hebben we gebruik gemaakt van data van drie poliklinieken, waarvan twee in een academische en één in een perifere setting. De voorschrijfindicatoren gericht op niet-calciumhoudende of calciumhoudende fosfaatbinders zijn niet berekend vanwege het beperkte aantal geïncludeerde patiënten. Daarnaast waren de uitslagen van de albumine/creatinine ratio maar in beperkte mate beschikbaar. Daarom zijn de indicatoren gericht op het voorschrijven van RAAS-remmers in de aanwezigheid van diabetes en microalbuminurie niet berekend, en is proteïnurie gebruikt als proxy voor macroalbuminurie. De resultaten lieten zien dat RAAS-remmers en statines relatief weinig werden voorgeschreven wanneer aanbevolen in de richtlijn en dat er relatief veel mogelijk ongepaste actieve vitamine D werd voorgeschreven. Daarnaast zijn er verschillen waargenomen tussen de CNS stadia. Patiënten met hogere CNS stadia werden minder vaak voorgeschreven met RAAS-remmers, maar vaker met statines wanneer aanbevolen, en vaker met mogelijk ongepaste actieve vitamine D en ESA dan patiënten met CNS stadium 3. Verder hebben we ook verschillen gezien tussen de poliklinieken, zelfs na stratificatie gebaseerd op de CNS stadia. Uit deze studie bleek dat deze voorschrijfindicatoren te berekenen zijn met gebruik van de beschikbare gegevens van Ziekenhuis Informatie Systemen.

Tabel NS.1: Ontwikkelde voorschrijfindicatoren voor chronische nierschade en hun validiteit

Voorschrijfindicator	Validiteit: Inhouds-	Indruks-	Operationele 1ste†	Operationele 2de†	Voorspellende
Behandeling van hypertensie					
1. Het percentage patiënten met CNS stadium 4-5 tussen de 18 en 80 jaar met hypertensie‡, dat antihypertensiva krijgt voorgeschreven, tenzij onwenselijk vanwege een te lage diastolische bloeddruk (<70 mmHg)	√	√	√	√	0
2a. Het percentage patiënten met CNS stadium 3-5 tussen de 18 en 80 jaar met macroalbuminurie§ behandeld met meerdere antihypertensiva, dat een combinatie van een ACE-remmer of een ARB met een diureticum krijgt voorgeschreven	√	√	√	√¶	0
2b. Het percentage patiënten met CNS stadium 3-5 tussen de 18 en 80 jaar met microalbuminurie§ en diabetes# behandeld met meerdere antihypertensiva, dat een combinatie van een ACE-remmer of een ARB met een diureticum krijgt voorgeschreven	√	√	√	-	0
Behandeling van albuminurie					
3a. Het percentage patiënten met CNS stadium 3-5 tussen de 18 en 80 jaar met macroalbuminurie§, dat met een ACE-remmer of een ARB krijgt voorgeschreven.	√	√	√	√¶	0
3b. Het percentage patiënten met CNS stadium 3-5 tussen de 18 en 80 jaar met microalbuminurie§ en diabetes#, dat een ACE-remmer of een ARB krijgt voorgeschreven	√	√	√	-	0
Voorschriften van statines					
4. Het percentage patiënten met CNS stadium 3-5 tussen de 50 en 65 jaar, dat een statine krijgt voorgeschreven	√	√	√	√	0
Behandeling van mineraal- en botstoornis					
5. Het percentage patiënten met CNS stadium 3-5 tussen de 18 en 80 jaar met een verhoogd fosfaat (>1.49 mmol/l), dat een fosfaatbinder krijgt voorgeschreven	√	√	√††	√	0
6. Het percentage patiënten met CNS stadium 3-5 tussen de 18 en 80 jaar behandeld met fosfaatbinders en met een verhoogd calcium (>2.54 mmol/l), dat een niet-calciumhoudende fosfaatbinder krijgt voorgeschreven	√	√	√††	0	0
7. Het percentage patiënten met CNS stadium 3-5 tussen de 18 en 80 jaar behandeld met fosfaatbinders en met een verlaagd calcium (<2.10 mmol/l) dat een calciumhoudende fosfaatbinder krijgt voorgeschreven	√	√	√††	0	0
Medicatieveiligheid					

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Tabel NS.1: Ontwikkelde voorschrijfindicatoren voor chronische nierschade en hun validiteit (vervolg)

Voorschrijfindicator	Validiteit: Inhouds-	Indruks-	Operationele 1ste†	Operationele 2de†	Voorspellende
8. Het percentage patiënten met CNS stadium 3-5 18 jaar en ouder behandeld met RAAS-remmers, dat ten minste twee RAAS-remmers tegelijkertijd krijgt voorgeschreven (dubbele RAAS blokkade)	√	√	√	√	0
9. Het percentage patiënten met CNS stadium 3-5 18 jaar en ouder met een verhoogd calcium (>2.54 mmol/l), dat actieve vitamine D krijgt voorgeschreven	√	√	√††	√	0
10. Het percentage patiënten met CNS stadium 3-5 18 jaar en ouder met een hemoglobine boven de streefwaarde (≥7.5 mmol/l), dat erytropoëse-stimulerende middelen krijgt voorgeschreven	√	√	√	√	0
11. Het percentage patiënten met een eGFR <30ml/min/1.73m^2 18 jaar en ouder, dat een NSAID krijgt voorgeschreven	√	√	√	√	0
12. Het percentage patiënten met een eGFR <30 ml/min/1.73m^2 18 jaar en ouder met diabetes#, dat metformine krijgt voorgeschreven	√	√	√	√	0
13. Het percentage patiënten met een eGFR <50 ml/min/1.73m^2 18 jaar en ouder, dat een hoge dosering digoxine (>0,125 mg/dag) krijgt voorgeschreven	√	√	√	√	0
14. Het percentage patiënten met CNS stadium 3-5 18 jaar en ouder, dat een combinatie van NSAIDs, RAAS-remmers en diuretica krijgt voorgeschreven	√	√	√	√	0

CNS: chronische nierschade; ACE-remmer: angiotensine-converterend-enzym remmer; ARB: angiotensine-II-receptorblokkers; RAAS: renine-angiotensine-aldosteronsysteem; eGFR: geschatte glomerulaire filtratie snelheid; NSAID: niet-steroïde anti-inflammatoire geneesmiddel.

† 1ste: eerstelijnszorg, 2de: tweedelijnszorg. ‡ Hypertensie is gedefinieerd als een systolische bloeddruk >140 mmHg of een voorschrift van een antihypertensiva. § Micro-albuminurie is gedefinieerd als albumine/creatinine ratio ≥3.0 mg/mmol en < 30 mg/mmol. Macro-albuminurie is gedefinieerd als albuminurie/creatinine ratio ≥30 mg/mmol. ¶ Deze indicatoren zijn getest met proteïnurie als proxy voor macroalbuminurie, aangezien de albumine/creatinine ratio's maar beperkt beschikbaar waren. # Diabetes is gedefinieerd als ofwel een diagnose voor diabetes of een voorschrift voor bloedglucose-verlagende middelen. †† Deze indicatoren zijn operationeel valide, maar includeerde <2% van de gehele patiëntpopulatie en zijn daardoor voornamelijk geschikt voor interne evaluatie. Inhoudsvaliditeit: √ = ontwikkeld gebaseerd op de richtlijnen. Indruks-/operationele/voorspellende validiteit: √ = getest en valide; - = getest en niet valide; 0 = niet getest.

Daarom kunnen we concluderen dat deze aangepaste set van voorschrijfindicatoren ook operationele validiteit heeft in de tweedelijnszorg (tabel NS.1).

Deel II: Kwaliteit van voorschrijven bij T2D

De doelstellingen van het tweede deel van dit proefschrift zijn (I) het ontwikkelen en valideren van een nieuwe set voorschrijfindicatoren voor T2D eerstelijnszorg, met speciale focus op actie-indicatoren, (II) het testen van mogelijke associaties tussen deze voorschrijfindicatoren en gezondheidsgerelateerde procesmaten en (III) het testen op mogelijke associaties tussen enkele voorschrijfindicatoren, medicatielast en kwaliteit van leven bij T2D patiënten.

Een set van twintig voorschrijfindicatoren voor diabeteszorg is ontwikkeld met behulp van een deskundig panel van internisten en huisartsen (**Hoofdstuk 5**). De set bestaat uit voorschrijfindicatoren die zich richten op de behandeling met bloedglucose-verlagende middelen, antihypertensiva, RAAS-remmers en statines wanneer aanbevolen, op mogelijke ongepast voorschrijven van glibenclamide, metformine en dubbele RAAS-blokkade, en mogelijke overbehandeling met bloedglucose-verlagende middelen bij ouderen. Acht van deze voorschrijfindicatoren zijn actie-indicatoren die zich richten op het tijdig starten of intensiveren van de aanbevolen behandeling. Tijdens de ontwikkeling zijn verscheidene indicatoren verworpen, zoals de volume-indicatoren over het gebruik van bloedglucose-verlagende middelen en de voorschrijfindicatoren gericht op het aanbevolen voorschrijven van bloedglucose-verlagende middelen bij oudere T2D patiënten, de voorkeur voor simvastatine, het starten van antihypertensiva gestratificeerd naar leeftijd en bloeddruk, het mogelijk ongepast voorschrijven van een combinatie van pioglitazon en insuline, het intensiveren van antihypertensiva in oudere T2D patiënten, het monitoren van het kalium wanneer RAAS-remmers of diuretica zijn voorgeschreven, het vaccineren tegen de griep en therapietrouw met betrekking tot bloedglucose-verlagende middelen, lipide-verlagende middelen en antihypertensiva. Na de ontwikkeling is de set getest in twee databases met T2D patiënten in de eerstelijnszorg (GIANTT en Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC)). De resultaten toonden aan dat alle twintig voorschrijfindicatoren berekend kunnen worden aan de hand van de beschikbare gegevens. Een aantal voorschrijfindicatoren includeerden echter een klein aantal patiënten door beperkte beschikbaarheid van gegevens. Door de gestructureerde ontwikkeling en op basis van deze resultaten kunnen we concluderen dat deze set van voorschrijfindicatoren voor T2D, inhouds-, indruks- en operationele validiteit heeft in de eerstelijnszorg (tabel NS.2).

Tabel NS.2: Ontwikkelde voorschrijfindicatoren voor type 2 diabetes en hun validiteit

	Validiteit			
Voorschrijfindicator	**Inhouds-**	**Indruks-**	**Operationele**	**Voorspellende**†
Bloedglucose-verlagende middelen				
1. Het percentage patiënten met T2D tussen de 18 en 70 jaar met een verhoogde HbA_{1c} waarde (>53 mmol/mol) in voorgaand jaar, waarbij gestart is met bloedglucose-verlagende middelen of de HbA_{1c} streefwaarde (≤53 mmol/mol) is behaald	√	√	√‡	√
2. Het percentage patiënten met T2D tussen de 18 en 70 jaar behandeld met metformine monotherapy met een verhoogde HbA_{1c} waarde (>53 mmol/mol) in voorgaand jaar, waarbij geïntensiveerd is met bloedglucose-verlagende middelen of de HbA_{1c} streefwaarde (≤53 mmol/mol) is behaald	√	√	√	√
3. Het percentage patiënten met T2D tussen de 18 en 70 jaar behandeld met twee of meer niet-insuline bloedglucose-verlagende middelen met een verhoogde HbA_{1c} waarde (>53 mmol/mol) in voorafgaand jaar, waarbij gestart is met insuline of de HbA_{1c} streefwaarde (≤53 mmol/mol) is behaald	√	√	√	√
4. Het percentage patiënten met T2D 18 jaar en ouder, waarbij gestart is met metformine binnen alle starters met orale bloedglucose-verlagende middelen	√	√	√	0
5. Het percentage patiënten met T2D 18 jaar en ouder behandeld met bloedglucose-verlagende middelen, dat metformine krijgt voorgeschreven	√	√	√	0
6. Het percentage patiënten met T2D 18 jaar en ouder behandeld met twee niet-insuline bloedglucose-verlagende middelen, dat een combinatie van metformine en een SU-derivaat krijgt voorgeschreven	√	√	√	0
7. Het percentage patiënten met T2D 18 jaar en ouder, waarbij gestart is met gliclazide binnen alle starters met SU-derivaten	√	√	√	0
Lipide-verlagende middelen				
8. Het percentage patiënten met T2D tussen de 55 en 80 jaar, dat een statine krijgt voorgeschreven	√	√	√	√

Tabel NS.2: Ontwikkelde voorschrijfindicatoren voor type 2 diabetes en hun validiteit (vervolg)

	Validiteit			
Voorschrijfindicator	**Inhouds-**	**Indruks-**	**Operationele**	**Voorspellende**[†]
9. Het percentage patiënten met T2D tussen de 18 en 80 jaar met een verhoogde LDL-cholesterol waarde (>2.5 mmol/l) in voorafgaand jaar, waarbij gestart is met een statine of de LDL-cholesterol streefwaarde (≤2.5 mmol/l) is behaald	√	√	√	√
10. Het percentage patiënten met T2D tussen de 18 en 80 jaar behandeld met simvastatine en met een verhoogde LDL-cholesterol waarde (>2.5 mmol/l) in voorafgaand jaar, waarbij overgestapt is naar atorvastatine or rosuvastatine of de LDL-cholesterol streefwaarde (≤2.5 mmol/l) is behaald	√	√	√	√
Antihypertensiva				
11. Het percentage patiënten met T2D tussen de 18 en 70 jaar met een verhoogde bloeddruk (>140 mmHg) in voorafgaand jaar, waarbij gestart is met antihypertensiva of de bloeddruk streefwaarde (≤140 mmHg) is behaald	√	√	√	√
12. Het percentage patiënten met T2D tussen de 18 en 70 jaar behandeld met antihypertensiva monotherapie en met een verhoogde bloeddruk (>140 mmHg) in voorafgaand jaar, waarbij geïntensiveerd is met antihypertensiva of de bloeddruk streefwaarde (≤140 mmHg) is behaald	√	√	√	√
Albuminurie-verlagende middelen				
13. Het percentage of patiënten met T2D 18 jaar en ouder behandeld met twee of meer antihypertensiva, dat een ACE-remmer of ARB krijgt voorgeschreven	√	√	√	-
14. Het percentage patiënten met T2D tussen de 18 en 70 jaar met micro- of macroalbuminurie[§] in voorafgaand jaar, waarbij gestart is met een ACE-remmer of ARB of teruggekeerd is naar normoalbuminurie[§]	√	√	√[‡]	√
15. Het percentage patiënten met T2D 18 jaar en ouder behandeld met antihypertensiva en met micro- of macroalbuminurie[§], dat een ACE-remmer of ARB krijgt voorgeschreven	√	√	√	-

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Tabel NS.2: Ontwikkelde voorschrijfindicatoren voor type 2 diabetes en hun validiteit (vervolg)

	Validiteit			
Voorschrijfindicator	**Inhouds-**	**Indruks-**	**Operationele**	**Voorspellende†**
16. Het percentage patiënten met T2D 18 jaar en ouder, waarbij gestart is met een ACE-remmer binnen alle starters van een RAAS behandeling	√	√	√	0
Medicatieveiligheid				
17. Het percentage patiënten met T2D 18 jaar en ouder behandeld met SU-derivaten, dat glibenclamide krijgt voorgeschreven	√	√	√	0
18. Het percentage patiënten met T2D 18 jaar en ouder met een eGFR <30 ml/min/1.73m^2, dat metformine krijgt voorgeschreven	√	√	√‡	0
19. Het percentage patiënten met T2D 80 jaar en ouder met een normale HbA_{1c} waarde (<53 mmol/mol), dat twee of meer bloedglucose-verlagende middelen krijgt voorgeschreven	√	√	√	0
20. Het percentage patiënten T2D 18 jaar en ouder behandeld met RAAS-remmers, dat een combinatie van een ACE-remmer en een ARB (dubbele RAAS blokkade) krijgt voorgeschreven	√	√	√	0

T2D: type 2 diabetes; HbA_{1c}: geglyceerd hemoglobine; SU-derivaat: sulfonylureumderivaat; LDL-cholesterol: lage dichtheid (low-density) lipoproteïne cholesterol; ACE-remmer: angiotensine-converterend-enzym remmer; ARB: angiotensine-II-receptorblokker; RAAS: renine-angiotensine-aldosteronesysteem; eGFR: geschatte glomerulaire filtratiesnelheid.
† Voorspellende validiteit met procesmaten. ‡ Deze indicatoren zijn operationeel valide, maar includeerde <2% van de gehele patiëntpopulatie en zijn daardoor voornamelijk geschikt voor interne evaluatie. § Micro- of macro-albuminurie is gedefinieerd als albumine/creatinine ratio ≥2.5 mg/mmol voor mannen en ≥3.5 mg/mmol voor vrouwen. Normo-albuminurie is gedefinieerd als albumine/creatinine ratio <2.5 mmol/l voor mannen en <3.5 mmol/l voor vrouwen. Inhoudsvaliditeit: √ = ontwikkeld gebaseerd op de richtlijnen. Indruks-/operationele/voorspellende validiteit: √ = getest en valide; - = getest en niet valide; 0 = niet getest.

Daarna zijn verschillende voorschrijfindicatoren getest op mogelijke associaties met klinische uitkomsten (**Hoofdstuk 6**). Voor deze studie zijn elf voorschrijfindicatoren geselecteerd waarvan op basis van de literatuur verwacht kan worden dat er invloed is op de bloedglucose-, cholesterol- of bloeddrukspiegel, of de prevalentie van albuminurie. Elf indicatoren zijn getest, waarvan acht actie-indicatoren, één indicator op het huidig gebruik van statines en twee indicatoren op het huidig gebruik van RAAS-remmers. De resultaten toonden aan dat de actie-indicatoren voor bloedglucose-verlagende middelen een jaar later significant geassocieerd waren met lagere bloedglucosespiegels. Evenzo bleken zowel beide actie-indicatoren als de indicator gericht op huidig gebruik van statines, beide actie-indicatoren gericht op antihypertensiva en de actie-indicator gericht op RAAS-remmers significant geassocieerd te zijn met respectievelijk lagere cholesterolspiegels, lagere bloeddruk en een lager risico op het hebben van albuminurie. De twee indicatoren gericht op het huidig gebruik van RAAS-remmers waren een jaar later niet geassocieerd met het risico op albuminurie. Gebaseerd op deze resultaten concluderen we dat alle geteste voorschrijfindicatoren, met uitzondering van de twee indicatoren op huidig gebruik van RAAS-remmers, voorspellende validiteit met procesmaten hebben. Dit betekent dat patiënten die behandeld worden volgens de voorschrijfindicatoren, een jaar later betere bloedglucose-, cholesterol- en bloeddrukspiegels hebben en een lager risico op albuminurie (tabel NS.2).

Tenslotte zijn mogelijke associaties tussen voorschrijven volgens de richtlijnen en diabetes-specifieke medicatielast met gezondheidsgerelateerde kwaliteit van leven in T2D patiënten onderzocht (**Hoofdstuk 7**). Voor het beoordelen van het voorschrijven volgens de richtlijnen zijn zeven voorschrijfindicatoren geselecteerd. Deze selectie is gebaseerd op de beschikbaarheid van de gegevens van de patiënten in de e-Vita/ZODIAC studie. Voor de meeste van de patiënten waren data van meerdere jaren niet beschikbaar en berekening van de actie-indicatoren was daardoor niet haalbaar. De drie indicatoren gericht op het huidig gebruik van statines en RAAS-remmers wanneer aanbevolen en vier voorschrijfindicatoren gericht op het ongepast voorschrijven van glibenclamide, metformine, dubbele RAAS-blokkade en overbehandeling van bloedglucose-verlagende middelen bij oudere T2D patiënten werden geselecteerd. Diabetes-gerelateerde medicatielast werd berekend met behulp van een aangepaste Medication Regimen Complexity Index. Hierbij wordt een score berekend gebaseerd op het aantal voorschriften en de complexiteit van de voorschriften. Onder diabetes-gerelateerde medicatie werden bloedglucose-verlagende middelen, statines en antihypertensiva gerekend. De kwaliteit van leven werd beoordeeld door middel van de Euroqol 5 dimensions 3 levels (EQ5F-3L) vragenlijst en de World Health Organization Well-Being Index. Beide vragenlijsten zijn kort met vijf vragen, en geven een indicatie van respectievelijk de algemene en de mentale kwaliteit van leven. Een groot deel van de patiënten scoorde hoog op de EQ5D-3L en de uitkomst werd daarom gedichotomiseerd. Uit de resultaten blijkt dat voorschrijven volgens de richtlijnen beoordeeld met de zeven voorschrijfindicatoren niet geassocieerd is met kwaliteit van leven bij T2D patiënten. Er werd ook geen significante associatie gevonden tussen diabetes-gerelateerde medicatielast en kwaliteit van leven. Het vermogen van deze studie om associaties met kwaliteit van leven te detecteren was echter beperkt door het aantal geïncludeerde patiënten. Bovendien heeft het dichotomiseren van de EQ5D-3L het vermogen om associaties te detecteren verder verminderd. Daarom concluderen we dat er op dit moment geen bewijs is dat voorschrijven volgens de richtlijnen of diabetes-gerelateerde medicatielast de kwaliteit van leven van T2D patiënten beïnvloed.

Conclusie

Uit dit proefschrift komen twee sets van valide voorschrijfindicatoren voor de beoordeling van de kwaliteit van voorschrijven in CNS en T2D. Verscheidene van deze voorschrijfindicatoren zijn klaar voor implementatie in kwaliteitsverbeteringsinitiatieven, zoals audit-en-feedback-programma's. Sommige voorschrijfindicatoren moeten meer getest worden, vooral op voorspellende validiteit (tabel NS.1 en NS.2). Niettemin beschrijft dit proefschrift een aantal belangrijke stappen naar een betere beoordeling van de kwaliteit van voorschrijven en optimale farmacotherapie bij patiënten met CNS of T2D.

APPENDICES

Appendix 1: Supplemental data chapter 2

Table S2.1: Search strategy

Database	Search terms
Pubmed	
Quality of Health Care	(((process[tw] OR quality[tw] OR performance[tw] OR safety[tw]) AND (screen*[tw] OR monitor*[tw] OR care[tw] OR treatment[tw] OR therapy[tw] OR prescri*[tw] OR medicat*[tw])) OR "Quality of Health Care"[Mesh:noexp])
Quality Indicators	AND (assess*[tw] OR measur*[tw] OR indicator*[tw] OR criteria[tw] OR "Quality Indicators, Health Care"[Mesh:noexp])
Chronic kidney disease	AND (("Kidney Diseases"[Mesh:noexp] OR "Diabetic Nephropathies"[Mesh] OR "Hypertension, Renal"[Mesh] OR "Renal Insufficiency"[Mesh] OR "Renal Insufficiency, Chronic"[Mesh] OR kidney disease*[tw] OR renal disease*[tw] OR renal insufficiency[tw] OR nephropathy[tw]) NOT "Kidney Neoplasms"[Mesh])
Embase	
Quality of Health Care	(((process:ab,ti OR quality:ab,ti OR performance:ab,ti OR safety:ab,ti) AND (screen*:ab,ti OR monitor*:ab,ti OR care:ab,ti OR treatment:ab,ti OR therapy:ab,ti OR prescri*:ab,ti OR medicat*:ab,ti)) OR 'health care quality'/de)
Quality Indicators	AND (assess*:ab,ti OR measur*:ab,ti OR indicator*:ab,ti OR criteria:ab,ti)
Chronic kidney disease	AND (('kidney disease'/de OR 'kidney dysfunction'/exp OR 'kidney failure'/de OR 'chronic kidney disease'/exp OR 'diabetic nephropathy'/exp OR 'chronic kidney failure'/exp OR 'kidney disease':ab,ti OR 'renal disease':ab,ti ORnephropathy:ab,ti OR 'renal insufficiency':ab,ti OR 'kidney insufficiency':ab,ti OR 'renal diseases':ab,ti OR 'kidney diseases':ab,ti) NOT 'kidney tumor'/exp)

A

Table S2.2: Definitions of all indicators with their scoring on face, content, operational and predictive validity

Indicators
Monitoring
Measuring kidney function
GFR/eGFR in CKD patients
· The percentage of patients with stage 3-4 CKD annually tested for eGFR[1]
· The percentage of patients with stage 3 CKD with a measurement of eGFR every 6 months[2]
· The percentage of patients with stage 4 CKD with a measurement of eGFR every 3 months[2]
· The percentage of patients with CKD stage 3-4 with annual serum eGFR test[3]
Serum creatinine in CKD patients
· The percentage of patients with CKD with screening for creatinine[4]
Serum albumin in CKD patients
· The percentage of patients with CKD stage 3-5 that had their albumin level tested[5]
· The percentage of patients with CKD stage 3-5 and routine determination of serum albumin[6]
· The percentage of patients with two serum creatinine levels ≥1.7 mg/dl and CrCl <50 ml/min with measurements of serum albumin levels[7]
· The percentage of patients with CRI with screening of albumin[8]
ACR in CKD patients
· The percentage of patients with CKD stage 3-5 that had their ACR tested[5]
· The percentage of patients on the CKD register who have a record of urine albumin: creatinine ratio (or protein: creatinine ratio) test in the previous 15 months[9]
Urinary protein in CKD patients
· The percentage of patients with stage 3-4 CKD annually tested for urine protein[1]
· The percentage of patients with CKD stage 3-5 and routine determination of daily urinary measurements[6]
· The percentage of patients with two serum creatinine levels ≥1.7 mg/dl with a measurement of dipstick urinalysis for protein[7]
· The percentage of patients with two serum creatinine levels ≥1.7 mg/dl with measurement of urinary protein quantification[7]
· The percentage of patients with two eGFR <60 ml/min/$1.73m^2$ that had urine microalbumin measured at least annually[10]
· The percentage of patients with CKD with quantified proteinuria[11]
· The percentage of patients with eGFR <45 ml/min/$1.73m^2$ with urinary albumin tested at least once within 6 months following index eGFR <45 ml/min/$1.73m^2$ [12]
· The percentage of patients with CKD stage 3-4 with an annual urine albumin/protein test[3]
Urinary protein in CKD patients with comorbidities
· The percentage of patients with diabetes, ischaemic heart disease, hypertension and stage 3 CKD with a measurement of proteinuria[13]
· The percentage of patients with CKD and diabetes with screening for microalbumin[4]
· The percentage of patients with eGFR <60 ml/min/$1.73m^2$ with proteinuria monitored annually[2]

Inclusion criteria for CKD	Content validity	Face validity	Operational validity	Data source	Predictive validity
CKD 3-4	√	0	√	A	0
CKD 3	√	√	0		0
CKD 4	√	√	0		0
CKD 3-4	+	0	√	A	0
ICD-9-CM	x	0	√	A	0
CKD 3-5	x	0	√	A	0
CKD 3-5	√	Ø	√	C	0
Serum creatinine≥1.7 mg/dl and CrCl<50 ml/min	x	0	√	B	0
Serum creatinine≥1.5 mg/dl for women, ≥2.0 mg/dl for men	x	0	√	B	0
CKD 3-5	x	0	√	A	0
CKD 3-5	+	+	√	A	0
CKD 3-4	√	0	√	A	0
CKD 3-5	x	Ø	√	C	0
Serum creatinine≥1.7 mg/dl	x	0	√	B	0
Serum creatinine≥1.7 mg/dl	x	0	√	B	0
CKD 3-5	+	0	√	B	0
CKD 3	√	0	√	A	0
CKD 3b-5	√	0	√	A	0
CKD 3-4	+	0	√	A	0
CKD 3	√	0	√	A	0
ICD-9-CM	x	0	√	A	0
CKD 3-5	√	√	0		0

Table S2.2: Definitions of all indicators with their scoring on face, content, operational and predictive validity (continued)

Indicators
Measuring MBD
Serum phosphorus/phosphate
· The percentage of patients with CKD stage 3-5 that had their phosphate level tested[5]
· The percentage of patients with two serum creatinine levels ≥1.7 mg/dl and CrCl <50 ml/min with a measurement of serum phosphate levels[7]
· The percentage of patients with CRI with screening of phosphorus levels[8]
· The percentage of patients with evidence of impaired renal function with phosphorus measurement[14]
· The percentage of patients with CKD with phosphorus assessment[11]
· The percentage of patients with CKD stage 3-4 with an annual serum phosphorus test[3]
Serum calcium
· The percentage of patients with stage 3-4 CKD annually tested for calcium[1]
· The percentage of patients with CKD stage 3-5 that had their calcium level tested[5]
· The percentage of patients with two serum creatinine levels ≥1.7 mg/dl and CrCl <50 ml/min with a measurement of serum calcium levels[7]
· The percentage of patients with CRI with screening of serum calcium[8]
· The percentage of patients with evidence of impaired renal function with calcium measurement[14]
· The percentage of patients with CKD with calcium assessment[11]
· The percentage of patients with CKD stage 3-4 with an annual serum calcium test[3]
Serum iPTH
· The percentage of patients with stage 3-4 CKD annually tested for parathyroid hormone[1]
· The percentage of patients with CKD stage 3-5 that had their PTH level tested[5]
· The percentage of patients with CRI with screening of serum PTH[8]
· The percentage of patients with CKD with screening for PTH[4]
· The percentage of patients with evidence of impaired renal function with PTH measurement[14]
· The percentage of patients with CKD with iPTH assessment[11]
· The percentage of patients with CKD stage 3-4 with an annual serum parathyroid test[3]
Other
· The percentage of patients with stage 3-4 CKD annually tested for 25-hydroxyvitamin D[1]
· The percentage of patients with CKD stage 3-5 that had their vitamin D level tested[5]
· The percentage of patients with CKD with screening for calcium/phosphorus[4]
· The percentage of patients with two eGFR <45 ml/min/1.73m^2 that had vitamin D measurement (or vitamin D supplements initiated)[10]
Measuring anaemia

Inclusion criteria for CKD	Content validity	Face validity	Operational validity	Data source	Predictive validity
CKD 3-5	x	0	√	A	0
Serum creatinine≥1.7 mg/dl and CrCl<50 ml/min	x	0	√	B	0
Serum creatinine≥1.5 mg/dl for women, ≥2.0 mg/dl for men	x	0	√	B	0
Serum creatinine>1.3 mg/dl for women, >1.5 mg/dl for men	x	0	√	B	0
CKD 3	√	0	√	A	0
CKD 3-4	+	0	√	A	0
CKD 3-4	√	0	√	A	0
CKD 3-5	x	0	√	A	0
Serum creatinine≥1.7 mg/dl and CrCl <50 ml/min	x	0	√	B	0
Serum creatinine≥1.5 mg/dl for women, ≥2.0 mg/dl for men	x	0	√	B	0
Serum creatinine>1.3 mg/dl for women, >1.5 mg/dl for men	x	0	√	B	0
CKD 3	√	0	√	A	0
CKD 3-4	+	0	√	A	0
CKD 3-4	√	0	√	A	0
CKD 3-5	x	0	√	A	0
Serum creatinine≥1.5 mg/dl for women, ≥2.0 mg/dl for men	x	0	√	B	0
ICD-9-CM	x	0	√	A	0
Serum creatinine>1.3 mg/dl for women, >1.5 mg/dl for men	x	0	√	B	0
CKD 3	√	0	√	A	0
CKD 3-4	+	0	√	A	0
CKD 3-4	√	0	√	A	0
CKD 3-5	x	0	√	A	0
ICD-9-CM	x	0	√	A	0
CKD 3b-5	+	0	√	B	0

Table S2.2: Definitions of all indicators with their scoring on face, content, operational and predictive validity (continued)

Indicators
Haemoglobin in CKD patients
· The percentage of patients with stage 3-4 CKD annually tested for haemoglobin[1]
· The percentage of patients with CKD stage 3-5 that had their haemoglobin level tested[5]
· The percentage of patients with CKD using ESA that had their haemoglobin measured[15]
· The percentage of patients with two eGFR <45 ml/min/1.73m^2 that had haemoglobin measured annually[10]
· The percentage of patients with evidence of impaired renal function with haemoglobin measurement[14]
· The percentage of patients with CKD stage 3-4 with an annual serum haemoglobin/haematocrit test[3]
· The percentage of patients with CKD tested for serum haemoglobin[16]
Haemoglobin in CKD patients with comorbidities
· The percentage of patients with diabetes, ischaemic heart disease, hypertension and stage 3 CKD with a measurement of haemoglobin[13]
Iron
· The percentage of patients with CKD stage 3-5 that had their iron level tested[5]
· The percentage of patients with CRI with screening of iron studies[8]
· The percentage of patients with CKD with screening for iron levels[4]
· The percentage of patients with evidence of impaired renal function with iron parameters measurement[14]
Haematocrit
· The percentage of patients with two serum creatinine levels ≥1.7 mg/dl and CrCl <50 ml/min with measurements of serum haematocrit levels[7]
· The percentage of patients with CRI with screening of haematocrit[8]
Other
· The percentage of patients with CKD stage 3-5 that had their total iron binding capacity tested[5]
· The percentage of patients with CKD stage 3-5 that had their ferritin level tested[5]
· The percentage of patients with CKD using ESA that had their ferritin and TSAT measured[15]
· The percentage of patients with CKD with screening for anaemia[4]
· The percentage of patients with CKD stage 3b-5 (eGFR <45 ml/min/1.73m^2) with a complete blood count measured annually[2]
Measuring lipid levels
Lipid levels in CKD patients
· The percentage of patients with stage 3-4 CKD annually tested for LDL-cholesterol[1]
· The percentage of patients with CRI with screening of LDL-cholesterol[8]

Inclusion criteria for CKD	Content validity	Face validity	Operational validity	Data source	Predictive validity
CKD 3-4	√	0	√	A	0
CKD 3-5	x	0	√	A	0
CKD 1-5	+	0	√	A	0
CKD 3b-5	+	0	√	B	0
Serum creatinine>1.3 mg/dl for women, >1.5 mg/dl for men	x	0	√	B	0
CKD 3-4	+	0	√	A	0
CKD 3-5	-	0	√	A	0
CKD 3	+	+	√	A	0
CKD 3-5	x	0	√	A	0
Serum creatinine≥1.5 mg/dl for women, ≥2.0 mg/dl for men	x	0	√	B	0
ICD-9-CM	x	0	√	A	0
Serum creatinine>1.3 mg/dl for women, >1.5 mg/dl for men	x	0	√	B	0
Serum creatinine≥1.7 mg/dl and CrCl<50 ml/min	x	0	√	B	0
Serum creatinine≥1.5 mg/dl for women, ≥2.0 mg/dl for men	x	0	√	B	0
CKD 3-5	x	0	√	A	0
CKD 3-5	x	0	√	A	0
CKD 1-5	+	0	√	A	0
ICD-9-CM	x	0	√	B	0
CKD 3b-5	√	√	0		0
CKD 3-4	√	0	√	A	0
Serum creatinine≥1.5 mg/dl for women, ≥2.0 mg/dl for men	x	0	√	B	0

A

Table S2.2: Definitions of all indicators with their scoring on face, content, operational and predictive validity (continued)

Indicators
· The percentage of patients with CRI with screening of cholesterol[8]
· The percentage of patients with CRI with screening of triglycerides[8]
· The percentage of patients with CKD with screening for lipids[4]
· The percentage of patients with CKD with a lipid panel in the past year[2]
· The percentage of patients with two eGFR <60 ml/min/1.73m^2 that had LDL-cholesterol measured at least annually[10]
· The percentage of patients with evidence of impaired renal function with serum cholesterol level measurement[14]
· The percentage of patients with CKD with lipid assessment[11]
· The percentage of patients with CKD stage 3-4 with an annual LDL test[3]
Lipid levels in CKD patients with comorbidities
· The percentage of patients with diabetes, ischaemic heart disease, hypertension and stage 3 CKD with a measurement of LDL-cholesterol[13]
Measuring HbA$_{1c}$
HbA$_{1c}$ in CKD patients
· The percentage of patients with CKD stage 3-5 that had their A$_{1c}$ tested[5]
· The percentage of patients with two serum creatinine levels ≥1.7 mg/dl with a measurement of HbA$_{1c}$[7]
· The percentage of patients with two eGFR <60 ml/min/1.73m^2 that had A$_{1c}$ measured at least annually[10]
HbA$_{1c}$ in CKD patients with diabetes
· The percentage of patients with CRI and diabetes with screening of HbA$_{1c}$[8]
· The percentage of patients with CKD and diabetes with screening for HbA$_{1c}$[4]
· The percentage of patients with eGFR <45 ml/min/1.73m^2 with glycated haemoglobin tested at least annually[12]
HbA$_{1c}$ in CKD patients with comorbidities
· The percentage of patients with diabetes, ischaemic heart disease, hypertension and stage 3 CKD with a measurement of HbA$_{1c}$[13]
Measuring blood pressure
Blood pressure in CKD patients
· The percentage of patients with CKD with blood pressure recorded in 6 months[2]
· The percentage of patients on the CKD register whose notes have a record of blood pressure in the previous 15 months[17]
· The percentage of patients in the British Forces Germany health services primary care on the CKD register whose notes have a record of blood pressure in the previous 15 months[18]
Blood pressure in CKD patients with comorbidities

Inclusion criteria for CKD	Content validity	Face validity	Operational validity	Data source	Predictive validity
Serum creatinine≥1.5 mg/dl for women, ≥2.0 mg/dl for men	x	0	√	B	0
Serum creatinine≥1.5 mg/dl for women, ≥2.0 mg/dl for men	x	0	√	B	0
ICD-9-CM	x	0	√	A	0
CKD	√	√	0		0
CKD 3-5	+	0	√	B	0
Serum creatinine>1.3 mg/dl for women, >1.5 mg/dl for men	x	0	√	B	0
CKD 3	√	0	√	A	0
CKD 3-4	+	0	√	A	0
CKD 3	√	0	√	A	0
CKD 3-5	x	0	√	A	0
Serum creatinine≥1.7 mg/dl	x	0	√	B	0
CKD 3-5	+	0	√	B	0
Serum creatinine≥1.5 mg/dl for women, ≥2.0 mg/dl for men	x	0	√	B	0
ICD-9-CM	x	0	√	A	0
CKD 3b-5	√	0	√	A	0
CKD 3	√	0	√	A	0
CKD	√	√	0		0
CKD 3-5	+	+	√	A	0
CKD 3-5	+	Ø	0		0

A

Table S2.2: Definitions of all indicators with their scoring on face, content, operational and predictive validity (continued)

Indicators
· The percentage of patients with diabetes, ischaemic heart disease, hypertension and stage 3 CKD with a measurement of blood pressure[13]
Measuring body composition
· The percentage of patients with CKD stage 3-5 and routine determination of body weight/body mass index[6]
· The percentage of patients with CKD stage 3-5 and routine determination of subjective global assessment (nutritional assessment)[6]
· The percentage of patients with CKD stage 3-5 and routine determination of skinfold thickness[6]
· The percentage of patients with CKD stage 3-5 and routine determination of bioimpedance analysis[6]
Measuring diet
· The percentage of patients with CKD stage 3-5 and routine determination of nutrient levels[6]
Other measurements
· The percentage of patients with evidence of impaired renal function with plasma homocysteine/C-reactive protein level measurement[14]
Treatment
Treatment with ACE-i/ARB
Use of ACE-i/ARBs in CKD patients
· The percentage of patients with CKD stage 3-5 that were prescribed with RAAS inhibitors[5]
· The percentage of patients with CKD stage 3-5 that were prescribed an ACE-i/ARB[19]
· The percentage of patients with albuminuria (≥30 mg/24 h or 20 mg/l), or clinical proteinuria (≥300 mg/24 h or ≥20 mg/l), or a positive proteinuria dipstick receiving ACE-i/ARBs[20]
· The percentage of patients with CKD stage 3-5 on ACE-i[21]
· The percentage of patients with CKD stage 3-5 on ARBs[21]
· The percentage of patients with two serum creatinine levels ≥1.7 mg/dl using ACE-i/ARB[7]
· The percentage of patients with CKD receiving ACE-i/ARBs, but no diuretics[22]
· The percentage of patients with CKD receiving ACE-i/ARBs and diuretics[22]
· The percentage of patients with CKD receiving ACE-i/ARBs (regardless of diuretic use)[22]
· The percentage of patients with CRI receiving ACE-i[8]
· The percentage of patients with CKD prescribed ACE-i/ARB[4]
· The percentage of patients with CKD stage 3-5 prescribed ACE-i or ARB in last year[23]
· The percentage of patients with two eGFR <60 ml/min/1.73m^2 that had ACE-i/ARB initiated[10]
· The percentage of patients with evidence of impaired renal function without intolerance for ACE-i/ARB receiving ACE-i/ARB[14]
· The percentage of patients with diabetes and eGFR <60 ml/min/1.73 m^2 with prescription of ACE-i or ARBs[24]
· The percentage of patients with CKD using ACE-i/ARBs[11]
· The percentage of patients with CKD stage 3-4 with an ACE-i/ARB prescription[3]

Inclusion criteria for CKD	Content validity	Face validity	Operational validity	Data source	Predictive validity
CKD 3	√	0	√	A	0
CKD 3-5	√	Ø	√	C	0
CKD 3-5	√	Ø	√	C	0
CKD 3-5	√	Ø	√	C	0
CKD 3-5	√	Ø	√	C	0
CKD 3-5	√	Ø	√	C	0
Serum creatinine>1.3 mg/dl for women, >1.5 mg/dl for men	x	0	√	B	0
CKD 3-5	x	0	√	A	0
CKD 3-5	√	0	√	A	0
Albuminuria/ proteinuria	√	0	√	A	0
CKD 3-5	x	0	√	B	0
CKD 3-5	x	0	√	B	0
Serum creatinine≥1.7 mg/dl	x	0	√	B	0
CKD 1-5	x	0	√	A	0
CKD 1-5	x	0	√	A	0
CKD 1-5	x	0	√	A	0
Serum creatinine≥1.5 mg/dl for women, ≥2.0 mg/dl for men	x	0	√	B	0
ICD-9-CM	x	0	√	A	0
CKD 3-5	√	0	√	A	0
CKD 3-5	+	0	√	B	0
Serum creatinine>1.3 mg/dl for women, >1.5 mg/dl for men	x	0	√	B	0
CKD 3-5	x	0	√	B	0
CKD 3	√	0	√	A	0
CKD 3-4	+	0	√	A	0

A

Table S2.2: Definitions of all indicators with their scoring on face, content, operational and predictive validity (continued)

Indicators
· The percentage of patients with CKD using ACE-i or ARBs[25]
· The percentage of patients with CRI using ACE-i[26]
· The percentage of patients with CRI using ARBs[26]
· The percentage of patients with CrCl <75 ml/min documented at least twice not prescribed with ACE-i/ARB[27]
Undertreatment of ACE-i/ARBs in CKD patients
· The percentage of patients with CrCl <60 ml/min receiving too low a dose of ACE-i/ARB to benefit from its optimal nephroprotective effect[28]
ACE-i/ARBs in CKD patients with hypertension
· The percentage of patients with CKD stage 3-5 and hypertension that received an ACE-i[19]
· The percentage of patients with CKD stage 3-5 and hypertension that received an ARB[19]
· The percentage of patients with CKD stage 3-5 and hypertension that received an ACE-i and/or ARB[19]
· The percentage of patients with both blood pressure ≥130/80 mmHg and eGFR <60 ml/min/1.73m^2, regardless of albuminuria/proteinuria status receiving ACE-i/ARBs[20]
· The percentage of patients on the CKD register with hypertension and proteinuria who are treated with an ACE-i or ARB (unless a contraindication of side effect are recorded)[9]
· The percentage of patients on the CKD register with hypertension taking with an ACE-i/ARB[29]
· The percentage of patients on the CKD register with hypertension and proteinuria who are treated with an ACE-i/ARB[30]
· The percentage of patients on the CKD register with hypertension who are treated with an ACE-i or ARB – unless a contraindication or side effects are recorded[17]
· The percentage of patients on the CKD register with hypertension who are treated with an ACE-i or ARB – unless a contraindication or side effects are recorded[18]
ACE-i/ARBs in CKD patients with diabetes
· The percentage of patients with CKD stage 3-5 and diabetes that were prescribed an ACE-i/ARB[19]
· The percentage of patients with CrCl <60 ml/min and diabetic neuropathy not receiving an ACE-i or ARB to slow progression of his chronic kidney disease[28]
· The percentage of patients with eGFR <45 ml/min/1.73 m^2 with at least one prescription of an ACE-i or ARB among patients >66 year with diabetes or significant proteinuria[12]
· The percentage of patients with diabetes and proteinuria who are prescribed ACE-i/ARB[31]
ACE-i/ARBs in CKD patients with multiple comorbidities
· The percentage of patients with stage 3-4 CKD and hypertension, diabetes, urine protein/creatinine ratio>0.15 or a spot urine albumin/creatinine ratio >30 mcg/mg and no documented drug allergy prescribed ACE-i/ARBs during the previous 12 months[1]
· The percentage of patients with CKD stage 3-5 and presence of 1 comorbidity (diabetes, hypertension or dyslipidaemia) that were prescribed an ACE-i/ARB[19]
· The percentage of patients with CKD stage 3-5 and presence of 2 comorbidities (diabetes, hypertension or dyslipidaemia) that were prescribed an ACE-i/ARB[19]

Inclusion criteria for CKD	Content validity	Face validity	Operational validity	Data source	Predictive validity
CKD 1-4	√	0	√	C	0
CrCl<75 ml/min	x	0	√	B	0
CrCl<75 ml/min	x	0	√	B	0
CrCl<75 ml/min	√	0	√	C	0
CrCl<60 ml/min	√	-	√	B	0
CKD 3-5	√	0	√	A	0
CKD 3-5	√	0	√	A	0
CKD 3-5	√	0	√	A	0
CKD 3-5	√	0	√	A	0
CKD 3-5	+	+	√	A	0
CKD 3-5	+	+	√	A	0
CKD 3-5	+	√	0		0
CKD 3-5	√	+	√	A	0
CKD 3-5	+	Ø	0		0
CKD 3-5	√	0	√	A	0
CrCl<60 ml/min	√	-	√	B	0
CKD 3b-5	√	0	√	A	0
Albuminuria/ proteinuria	√	0	√	A	0
CKD 3-4	√	0	√	A	0
CKD 3-5	√	0	√	A	0
CKD 3-5	√	0	√	A	0

A

Table S2.2: Definitions of all indicators with their scoring on face, content, operational and predictive validity (continued)

Indicators
· The percentage of patients with CKD stage 3-5 and presence of 3 comorbidities (diabetes, hypertension and dyslipidaemia) that were prescribed an ACE-i/ARB[19]
· The percentage of patients with CrCl <60 ml/min and non-diabetic neuropathy whose albumin/creatinine ratio is >2 mg/g and not receiving an ACE-i/ARB to slow progression of his chronic kidney disease[28]
· The percentage of patients with CKD, hypertension and proteinuria with a prescription of ACE-i or ARB recorded in the past year[2]
· The percentage of patients with diabetes, hypertension and proteinuria who are prescribed ACE-i/ARB[31]
Treatment with other antihypertensives
Beta blocking agents in CKD patients
· The percentage of patients with CKD stage 3-5 on beta-blocker[21]
· The percentage of patients with CRI using β-adrenergic blockers[26]
Beta blocking agents in CKD patients with diabetes
· The percentage of patients with diabetes and eGFR <60 ml/min/1.73 m^2 with prescription of β-bockers[24]
Calcium channel blocker in CKD patients
· The percentage of patients with CKD stage 3-5 on calcium channel blocker[21]
Calcium channel blocker in CKD patients with diabetes
· The percentage of patients with diabetes and eGFR <60 ml/min/1.73 m^2 with prescription of calcium channel blockers[24]
Diuretics in CKD patients
· The percentage of patients with CKD stage 3-5 that were prescribed aldosterone antagonists[5]
· The percentage of patients with CKD stage 3-5 that were prescribed a loop diuretic[5]
· The percentage of patients with CKD receiving diuretics, but no ACE-i/ARBs[22]
Antihypertensive treatment in CKD patients
· The percentage of patients with CKD receiving antihypertensives[22]
· The percentage of patients with stage 3-5 CKD and hypertension taking two or more antihypertensive medication[29]
· The percentage of patients with CRI receiving non-ACE-i antihypertensive medications[8]
· The percentage of patients with CKD prescribed antihypertensive drugs[4]
Not receiving antihypertensive treatment in CKD patients
· The percentage of patients with CrCl <60 ml/min and a blood pressure >130/80 with no prescription of antihypertensives[28]
· The percentage of patients with two serum creatinine levels ≥1.7 mg/dl not using antihypertensive agents[7]
· The percentage of patients with CKD receiving no ACE-i/ARBs and no diuretics[22]
· The percentage of patients with stage 3-5 CKD and hypertension receiving no treatment for blood pressure[29]

Inclusion criteria for CKD	Content validity	Face validity	Operational validity	Data source	Predictive validity
CKD 3-5	√	0	√	A	0
CrCl<60 ml/min	√	-	√	B	0
CKD	√	√	0		0
Albuminuria/ proteinuria	√	0	√	A	0
CKD 3-5	x	0	√	B	0
CrCl<75 ml/min	x	0	√	B	0
CKD 3-5	x	0	√	B	0
CKD 3-5	x	0	√	B	0
CKD 3-5	x	0	√	B	0
CKD 3-5	x	0	√	A	0
CKD 3-5	x	0	√	A	0
CKD 1-5	x	0	√	A	0
CKD 1-5	x	0	√	A	0
CKD 3-5	x	0	√	A	0
Serum creatinine≥1.5 mg/dl for women, ≥2.0 mg/dl for men	x	0	√	B	0
ICD-9-CM	x	0	√	A	0
CrCl<60 ml/min	√	√	√	B	0
Serum creatinine≥1.7 mg/dl	x	0	√	B	0
CKD 1-5	x	0	√	A	0
CKD 3-5	x	0	√	A	0

Table S2.2: Definitions of all indicators with their scoring on face, content, operational and predictive validity (continued)

Indicators
Wrong dose/not intensifying antihypertensive treatment in CKD patients
· The percentage of patients with CrCl <60 ml/min and a blood pressure >130/80 receiving too low a dose of antihypertensives[28]
· The percentage of patients with a CrCl <75 ml/min documented at least twice and a blood pressure ≥140/90 mmHg whose antihypertensive treatment was not intensified[27]
Treatment with lipid lowering drugs
Statins in CKD patients
· The percentage of patients with CKD stage 3-5 that were prescribed a statin[5]
· The percentage of patients with CKD stage 3-5 on HMG-CoA reductase inhibitor/statin[21]
· The percentage of patients with CKD receiving statins, but no ezetimibe[22]
· The percentage of patients with CKD receiving statins and ezetimibe[22]
· The percentage of patients with CRI using statins when there is hyperlipidemia[26]
Statins in CKD patients with elevated LDL-cholesterol
· The percentage of patients with stage 3-4 CKD, a LDL-cholesterol >100 mg/dl and no documented drug allergy prescribed statins during the last 12 months[1]
· The percentage of patients with CrCl <60 ml/min, LDL-cholesterol >2.0 mmol/L and not receiving statin for appropriate cardiovascular prevention[28]
· The percentage of patients with CrCl <60 ml/min and a LDL-cholesterol >2.0 mmol/L receiving too low a dose of statin[28]
· The percentage of patients with eGFR <45 ml/min/1.73m^2 with at least one prescription for a statin among patients aged >66 with at least one LDL value >2.5 mmol/l within 6 months of index eGFR <45 ml/min/1.73m^2 [12]
Lipid lowering drugs in CKD patients
· The percentage of patients with CKD receiving lipid-modifying therapies[22]
· The percentage of patients with CKD receiving ezetimibe but no statins[22]
· The percentage of patients with CKD receiving multiple lipid-modifying therapies[22]
· The percentage of patients with CKD prescribed lipid lowering agents[4]
· The percentage of patients with CKD stage 3-5 prescribed lipid lowering medication last year[23]
· The percentage of patients with CKD patients using lipid lowering agents[25]
Lipid lowering drugs in CKD patients with elevated LDL-cholesterol
· The percentage of patients with evidence of impaired renal function and cholesterol >200 mg/dl on lipid lowering agents[14]
Lipid lowering drugs in CKD patients with diabetes
· The percentage of patients with diabetes and eGFR <60 ml/min/1.73 m^2 with prescription of lipid lowering agents[24]
Not receiving lipid lowering treatment in CKD patients
· The percentage of patients with CKD receiving no statins and no ezetimibe[22]
Treatment related to anaemia
EPO in CKD patients

Inclusion criteria for CKD	Content validity	Face validity	Operational validity	Data source	Predictive validity
CrCl<60 ml/min	√	√	√	B	0
CrCl<75 ml/min	√	0	√	C	0
CKD 3-5	x	0	√	A	0
CKD 3-5	x	0	√	B	0
CKD 1-5	x	0	√	A	0
CKD 1-5	x	0	√	A	0
CrCl<75 ml/min	x	0	√	B	0
CKD 3-4	√	0	√	A	0
CrCl<60 ml/min	√	-	0		0
CrCl<60 ml/min	√	-	0		0
CKD 3b-5	√	0	√	A	0
CKD 1-5	x	0	√	A	0
CKD 1-5	x	0	√	A	0
CKD 1-5	x	0	√	A	0
ICD-9-CM	x	0	√	A	0
CKD 3-5	√	0	√	A	0
CKD 1-4	√	0	√	C	0
Serum creatinine>1.3 mg/dl for women, >1.5 mg/dl for men	x	0	√	B	0
CKD 3-5	√	0	√	B	0
CKD 1-5	x	0	√	A	0

A

Table S2.2: Definitions of all indicators with their scoring on face, content, operational and predictive validity (continued)

Indicators
· The percentage of patients with CKD stage 3-5 that were prescribed ESA[5]
· The percentage of patients with CKD stage 3-5 on EPO[21]
· The percentage of patients with CKD receiving ESA[22]
· The percentage of patients with CRI receiving rHuEPO therapy[8]
· The percentage of patients with diabetes and eGFR <60 ml/min/1.73 m^2 with prescription of EPO agents[24]
EPO in CKD patients with evidence for anaemia
· The percentage of patients with CrCl <60 ml/min, haemoglobin <1 g/L, all other causes of anaemia have been eliminated and not receiving a hematopoietic agent[28]
· The percentage of patients with two serum creatinine levels ≥1.7 mg/dl, CrCl <50 ml/min and haematocrit <33% using erythropoietin[7]
· The percentage of patients with evidence of impaired renal function and haemoglobin <11 g/dL on erythropoietin therapy[14]
Iron supplement in CKD patients
· The percentage of patients with CKD stage 3-5 on iron[21]
· The percentage of patients with CrCl <60 ml/min, taking an erythropoiesis regulating agent and not receiving iron supplement by IV or P.O.[28]
· The percentage of patients with CRI receiving iron[8]
Iron supplement in CKD patients with evidence for anaemia
· The percentage of patients with CKD using ESA that initiated iron therapy within 2 weeks after ferritin level less than 100 ng/ml or TSAT < 20%[15]
· The percentage of patients with CrCl <60 ml/min, receiving iron supplement by IV and his ferritin is >500 µg/L and the coefficient of transferrin saturation is >20% when measured at least 2 weeks after IV administration of iron[28]
· The percentage of patients with CrCl <60 ml/min, not being treated with a haematopoietic agent, a ferritin <100 µg/L or a transferrin saturation rate <2% and not receiving an iron supplement by IV or P.O.[28]
· The percentage of patients with evidence of impaired renal function and TSAT <20% on iron therapy[14]
Treatment related to MBD
Phosphate binders in CKD patients
· The percentage of patients with CKD stage 3-5 that were prescribed a phosphate binder[5]
· The percentage of patients with CrCl <60 ml/min receiving too low a dose of phosphate binder[28]
· The percentage of patients with CRI receiving phosphate binders[8]
Phosphate binders in CKD patients with high levels of phosphate

Inclusion criteria for CKD	Content validity	Face validity	Operational validity	Data source	Predictive validity
CKD 3-5	x	0	√	A	0
CKD 3-5	x	0	√	B	0
CKD 1-5	x	0	√	A	0
Serum creatinine≥1.5 mg/dl for women, ≥2.0 mg/dl for men	x	0	√	B	0
CKD 3-5	x	0	√	B	0
CrCl<60 ml/min	√	-	0		0
Serum creatinine≥1.7 mg/dl and CrCl<50 ml/min	x	0	√	B	0
Serum creatinine>1.3 mg/dl for women, >1.5 mg/dl for men	√	0	√	B	0
CKD 3-5	x	0	√	B	0
CrCl<60 ml/min	√	-	0		0
Serum creatinine≥1.5 mg/dl for women, ≥2.0 mg/dl for men	x	0	√	B	0
CKD 1-5	+	0	√	A	0
CrCl<60 ml/min	√	-	0		0
CrCl<60 ml/min	√	-	0		0
Serum creatinine>1.3 mg/dl for women, >1.5 mg/dl for men	√	0	√	B	0
CKD 3-5	x	0	√	A	0
CrCl<60 ml/min	√	-	0		0
Serum creatinine≥1.5 mg/dl for women, ≥2.0 mg/dl for men	x	0	√	B	0

Table S2.2: Definitions of all indicators with their scoring on face, content, operational and predictive validity (continued)

Indicators
· The percentage of patients with CrCl <60 ml/min and serum phosphate higher than normal values for a patients with chronic kidney disease despite an appropriate diet receiving a phosphate binder (calcium, sevelamer or lanthanum carbonate)[28]
· The percentage of patients with evidence of impaired renal function and serum phosphorous >4.5 mg/dl on phosphate binding therapy[14]
Phosphate binders in CKD patients with diabetes
· The percentage of patients with diabetes and eGFR <60 ml/min/1.73 m^2 with prescription of phosphate binders[24]
Vitamin D in CKD patients
· The percentage of patients with CKD stage 3-5 that were prescribed vitamin D[5]
· The percentage of patients with stage 3 or 4 CKD and serum 25(OH)D <75 nmol/l receiving vitamin D (cholecalciferol, calciferol)[28]
· The percentage of patients with CRI receiving calcitriol[8]
Vitamin D in CKD patients with hyperparathyroidism
· The percentage of patients with CrCl <60 ml/min and hyperparathyroidism receiving vitamin D (calcitriol or alfacalcidol)[28]
· The percentage of patients with CrCl <60 ml/min and hyperparathyroidism despite correcting modifiable risk factors receiving too low a dose of vitamin D (calcitriol or alfacalcidol)[28]
· The percentage of patients with evidence of impaired renal function and PTH >100 on vitamin D analog therapy[14]
Treatment with glucose lowering drugs in CKD patients with diabetes
· The percentage of patients with CrCl <60 ml/min and HbA_{1c} >7% despite an appropriate diet receiving hypoglycaemic drug therapy[28]
· The percentage of patients with diabetes and eGFR <60 ml/min/1.73 m^2 with prescription of oral hypoglycaemic[24]
· The percentage of patients with diabetes and eGFR <60 ml/min/1.73 m^2 with prescription of insulin[24]
· The percentage of patients with CKD and diabetes using hypoglycaemic medication[25]
Treatment with acetylsalicylic acid in CKD patients
· The percentage of patients with CKD stage 3-5 on aspirin[21]
· The percentage of patients with CRI using acetylsalicylic acid[26]
Treatment with diet
· The percentage of patients with CKD stage 3-4 prescribed a low protein diet (0.6-0.75 g protein per kg body weight per day[6]
· The percentage of patients with CKD stage 5 prescribed a very low protein diet (0.3-0.35 g protein per kg body weight per day[6]
Safety
Use of NSAIDs
· The percentage of patients with CKD stage 3-4 prescribed NSAIDs during the prior 12 months[1]

	Inclusion criteria for CKD	Content validity	Face validity	Operational validity	Data source	Predictive validity
	CrCl<60 ml/min	√	-	0		0
	Serum creatinine>1.3 mg/dl for women, >1.5 mg/dl for men	√	0	√	B	0
	CKD 3-5	x	0	√	B	0
	CKD 3-5	x	0	√	A	0
	CKD 3-4	√	-	0		0
	Serum creatinine≥1.5 mg/dl for women, ≥2.0 mg/dl for men	x	0	√	B	0
	CrCl<60 ml/min	√	-	0		0
	CrCl<60 ml/min	√	-	0		0
	Serum creatinine>1.3 mg/dl for women, >1.5 mg/dl for men	√	0	√	B	0
	CrCl<60 ml/min	√	-	0		0
	CKD 3-5	x	0	√	B	0
	CKD 3-5	x	0	√	B	0
	CKD 1-4	√	0	√	C	0
	CKD 3-5	x	0	√	B	0
	CrCl<75 ml/min	x	0	√	B	0
	CKD 3-4	x	Ø	√	C	0
	CKD 5	x	Ø	√	C	0

	CKD 3-4	√	0	√	A	0

A

Table S2.2: Definitions of all indicators with their scoring on face, content, operational and predictive validity (continued)

Indicators
· The percentage of patients with CKD stage 3-5 that were prescribed a NSAID[5]
· The percentage of patients with CrCl <60 ml/min receiving a medication that is not indicated, a non-steroidal anti-inflammatory drug[28]
· The percentage of patients with CKD stage 3-5 NSAIDs recorded in chart last year[23]
· The percentage of patients with CKD stage 3-5 with avoidance of NSAIDs or cyclooxygenase-2 (COX-2) inhibitors[2]
· The percentage of patients with two eGFR <60 ml/min/1.73m^2 that had NSAID use discontinues[10]
Use of inappropriate drugs
Inappropriate glucose lowering drugs in CKD patients
· The percentage of patients with CKD stage 3-4 prescribed glyburide during the prior 12 months[1]
· The percentage of patients with CKD stage 3-4 prescribed metformin during the prior 12 months[1]
· The percentage of patients with CrCl <25 ml/min receiving acarbose[28]
· The percentage of patients with CrCl <30 ml/min receiving metformin[28]
Inappropriate antibiotics in CKD patients
· The percentage of patients with CKD stage 3-4 prescribed nitrofurantoin during the prior 12 months[1]
· The percentage of patients with CrCl <60 ml/min receiving nitrofurantoin[28]
Inappropriate osteoporosis drugs in CKD patients
· The percentage of patients with CKD stage 3-4 and eGFR <35 ml/min/1.73m^2 prescribed alendronate during the prior 12 months[1]
· The percentage of patients with CKD stage 3-4 and eGFR <30 ml/min/1.73m^2 prescribed ibandronate during the prior 12 months[1]
· The percentage of patients with CKD stage 3-4 and eGFR <35 ml/min/1.73m^2 prescribed risedronate during the prior 12 months[1]
· The percentage of patients with CrCl <30 ml/min receiving bisphosphonate (alendronate, etidronate, risedronate)[28]
· The percentage of patients with eGFR <30 ml/min/1.73m^2 and avoidance of bisphosphonates[2]
Inappropriate nutritional supplements in CKD patients
· The percentage of patients with CrCl <60 ml/min receiving a vitamin A enriched multivitamin[28]
· The percentage of patients with CrCl <60 ml/min receiving garlic supplement[28]
Other inappropriate drugs in CKD patients
· The percentage of patients with CKD stage 3-4 and eGFR <50 ml/min/1.73m^2 prescribed terbinafine during the prior 12 months[1]
· The percentage of patients with CKD stage 3-4 prescribed one or more inappropriate drugs[1]
· The percentage of patients with CrCl <60 ml/min receiving meperidine[28]
· The percentage of patients with CrCl <60 receiving an antacid containing calcium, magnesium aluminium and/or sodium[28]
· The percentage of patients with CrCl <60 ml/min receiving a purgative not indicated for kidney[28]
· The percentage of patients with CrCl <60 ml/min receiving ginkgo biloba[28]

Inclusion criteria for CKD	Content validity	Face validity	Operational validity	Data source	Predictive validity
CKD 3-5	x	0	√	A	0
CrCl<60 ml/min	√	√	√	B	0
CKD 3-5	√	0	√	A	0
CKD 3-5	√	√	0		0
CKD 3-5	+	0	√	B	0
CKD 3-4	√	0	√	A	0
CKD 3-4	√	0	√	A	0
CrCl<25 ml/min	√	√	√	B	0
CrCl<30 ml/min	√	√	√	B	0
CKD 3-4	√	0	√	A	0
CrCl<60 ml/min	√	√	√	B	0
CKD 3-4	√	0	√	A	0
CKD 3-4	√	0	√	A	0
CKD 3-4	√	0	√	A	0
CrCl<30 ml/min	√	√	√	B	0
CKD 4-5	√	√	0		0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CKD 3-4	√	0	√	A	0
CKD 3-4	√	0	√	A	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0

Table S2.2: Definitions of all indicators with their scoring on face, content, operational and predictive validity (continued)

Indicators
· The percentage of patients with CrCl <60 ml/min receiving St. John's wort[28]
· The percentage of patients with CrCl <60 ml/min receiving liqourice root[28]
· The percentage of patients with CrCl <60 ml/min and metabolic acidosis (HCO3 <20 mmol/l) and not receiving bicarbonate of soda[28]
· The percentage of patients with CrCl <60 ml/min and hyperkalemia (K+ >5.5 mmol/l) receiving sodium polystyrene sulfonate[28]
Inappropriate dosages of drugs
Inappropriate dosages of anti-epileptic drugs in CKD patients
· The percentage of patients with CrCl <60 ml/min receiving too high a dose of gabapentin[28]
· The percentage of patients with CrCl <60 ml/min receiving too high a dose of pregabalin[28]
Inappropriate dosages of antivirals in CKD patients
· The percentage of patients with CrCl <60 ml/min receiving too high a dose of an antiviral (acyclovir, valacyclobir, famciclovir) according to the dosage-adjustment tables for kidney disease[28]
· The percentage of patients with CrCl <60 ml/min receiving too high a dose of neuraminidase inhibitor (e.g. oseltamivir) according to the dosage-adjustment tables for kidney disease[28]
Inappropriate dosages antifungals in CKD patients
· The percentage of patients with CrCl <60 ml/min receiving too high a dose of cephalosporin according to the dosage- adjustment tables for kidney disease[28]
· The percentage of patients with CrCl <60 ml/min receiving too high a dose of a triazole (e.g. fluconazole) according to the dosage-adjustment tables for kidney disease[28]
Inappropriate dosages of antibiotics in CKD patients
· The percentage of patients with CrCl <60 ml/min receiving too high a dose of penicillin according to the dosage-adjustment tables for kidney disease[28]
· The percentage of patients with CrCl <60 ml/min receiving too high a dose of quinolone according to the dosage-adjustment tables for kidney disease[28]
· The percentage of patients with CrCl <60 ml/min receiving too high a dose of a sulfamide according to the dosage-adjustment tables for kidney disease[28]
· The percentage of patients with CrCl <60 ml/min receiving too high a dose of a tetracycline according to the dosage-adjustment tables for kidney disease[28]
Inappropriate dosages of antigout preparations in CKD patients
· The percentage of patients with CrCl <60 ml/min receiving too high a dose of allopurinol[28]
· The percentage of patients with CrCl <50 ml/min receiving too high a dose of colchicine as prophylactic treatment for gout[28]
Inappropriate dosages of MBD drugs in CKD patients
· The percentage of patients with CrCl <60 ml/min receiving too high a dose of phosphate binder (calcium, sevelamer or lanthanum carbonate) since he has hyperphosphataemia (<0.87 mmol/l in stage 3/4, and <1.13 mmol/l in stage 5)[28]
· The percentage of patients with CrCl <60 ml/min receiving too high a dose of calcium carbonate since he had hypercalcaemia[28]

Inclusion criteria for CKD	Content validity	Face validity	Operational validity	Data source	Predictive validity
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	-	0		0
CrCl<60 ml/min	√	-	0		0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<50 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	-	0		0
CrCl<60 ml/min	√	-	0		0

A

Table S2.2: Definitions of all indicators with their scoring on face, content, operational and predictive validity (continued)

Indicators
· The percentage of patients with CrCl <60 ml/min and hypoparathyroidism, hypercalcaemia or hyperphosphataemia receiving too high a dose of vitamin D (calcitriol, alfacalcidol, cholecalciferol of calciferol)[28]
Other inappropriate dosages in CKD patients
· The percentage of patients with CrCl <60 ml/min receiving too high a dose of a beta-blocker according to the dosage-adjustment tables for kidney disease[28]
· The percentage of patients with CrCl <60 ml/min receiving too high a dose of fenofibrate nanocrystals[28]
· The percentage of patients with CrCl <50 ml/min receiving too high a dose of ranitidine[28]
· The percentage of patients with CrCl <30 ml/min receiving too high a dose of varenicline[28]
· The percentage of patients with CrCl <60 ml/min receiving too high a dose of an ascorbic acid supplement (vitamin C), a dose >25 mg/day[28]
· The percentage of patients with CrCl <60 ml/min and haemoglobin >130 g/L receiving too high a dose of an hematopoietic agent (darbepoetine alfa, epoetin alfa)[28]
Inappropriate combinations of drugs
· The percentage of patients with CrCl <60 ml/min experiencing a drug interaction between calcium carbonate and an antibiotic (tetracycline or fluorquinolone except moxifloxacin)[28]
· The percentage of patients with CrCl <60 ml/min experiencing a drug interaction between calcium and iron P.O. taken concomitantly[28]
· The percentage of patients with CrCl <60 ml/min experiencing a drug interaction between his phosphate binder (calcium carbonate, sevelamer or lanthanum) and levothyroxine[28]
· The percentage of patients with CrCl <60 ml/min experiencing a drug interaction between levelamer or lanthanum and ciprofloxacin[28]
Adherence and taking behaviour
· The percentage of patients with CrCl <60 ml/min that is non-adherent to the anaemia treatment since the patient received more than 120% or less than 80% of the required quantity of the drug over 90 days[28]
· The percentage of patients with CrCl <60 ml/min that is non-adherent to the antihypertensive treatment since the patient received more than 120% or less than 80% of the required quantity of the drug over 90 days[28]
· The percentage of patients with CrCl <60 ml/min that is non-adherent to the hypolipidaemic treatment since the patient received more than 120% or less than 80% of the required quantity of the drug over 90 days[28]
· The percentage of patients with CrCl <60 ml/min that is non-adherent to the treatment regulating the phosphocalcic metabolism since the patient received more than 120% or less than 80% of the required quantity of the drug over 90 days[28]
· The percentage of patients with CrCl <60 ml/min that is non-adherent to the diabetes treatment since the patient received more than 120% or less than 80% of the required quantity of the drug over 90 days[28]
· The percentage of patients with CrCl <60 ml/min not taking his phosphate binder (calcium carbonate, sevelamer or lanthanum) appropriately[28]

Inclusion criteria for CKD	Content validity	Face validity	Operational validity	Data source	Predictive validity
CrCl<60 ml/min	√	-	0		0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<50 ml/min	√	√	√	B	0
CrCl<30 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	-	0		0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0

A

Table S2.2: Definitions of all indicators with their scoring on face, content, operational and predictive validity (continued)

Indicators
· The percentage of patients with CrCl <60 ml/min not taking his vitamin D (calcitriol or alfacalcidol) appropriately[28]
· The percentage of patients with CrCl <60 ml/min not taking his sodium polylsturene sulfonate appropriately[28]
Referral
· The percentage of patients with CrCL <60 ml/min not receiving a referral for smoking cessation or follow-up[28]
· The percentage of patients with two serum creatinine levels ≥1.7 mg/dl for who a renal consultation was requested[7]
· The percentage of patients with eGFR <30 ml/min/1.73m^2 with a referral to a nephrologist[2]
· The percentage of patients with two eGFR <30 ml/min/1.73m^2 that is referred to a nephrologist[10]
· The percentage of patients with eGFR <45 ml/min/1.73m^2 with a visit to a specialist within 18 months of an index eGFR measurement of <45 ml/min/1.73m^2 [12]

CKD: chronic kidney disease; (e)GFR: (estimated) glomerular filtration rate; ICD-9-CM: International Classification of Disease, Ninth Revision, Clinical Modification; CrCl: creatinine clearance; ACR: albumin/creatinine-ratio; MBD: mineral and bone disorder; CRI: chronic renal impairment; (i)PTH: (intact) parathyroid hormone; ESA: erythropoiesis-stimulating agent; TSAT: transferrin saturation; LDL-cholesterol; low-density lipoprotein-cholesterol; HbA_{1c}: glycated haemoglobin; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor blocker; RAAS: renin-angiotensin-aldosterone system; EPO: erythropoietin; IV: intravenous (injection); P.O.: oral administration; NSAID: non-steroidal anti-inflammatory drug.

Content validity: x = source of indicators not known, + = previously developed based on guidelines, √ = developed based on guidelines, - = tested but assessed as insufficient by authors. Face validity/Operational validity: 0 = not tested, ∅ = not adequately tested, - = tested but not valid, + = previously tested and validated, √ = tested and valid. Operational validity, way of retrieving data: A = computerized review of medical records or administrative data, B = chart review by researchers, C = self-reported.

Inclusion criteria for CKD	Content validity	Face validity	Operational validity	Data source	Predictive validity
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
CrCl<60 ml/min	√	√	√	B	0
Serum creatinine ≥1.7 mg/dl	x	0	√	B	0
CKD 4-5	√	√	0		0
CKD 4-5	+	0	√	B	0
CKD 3b-5	√	0	√	A	0

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Appendix 2: Supplemental data chapter 3

File S3.1: Calculation of eligible patients

The number of eligible patients for indicator *i* was calculated using the formula:

$$n_n = \frac{Z_{a/2}^2 \cdot p_i(100 - p_i)}{d^2}$$

p_i reflects the observed performance score on indicator *i*, expressed as a percentage.

Z represents the standardised normal variate associated with the 95% confidence interval, which is 1.96.

d reflects the desired level of precision (margin of error) on $p_{i,}$ which was set at 10 percentage points for the medication need and medication choice indicators and at 5 percentage points for safety indicators with outcome >5% or 1 percentage point for safety indicators with outcome ≤5%.

Then n_n reflects the number of eligible patients needed to require the set level of precision for the outcome of the indicator.

When the p_i is closer to 100 or closer to 0, less eligible patients are needed, while a p_i closer to 50 will result in a larger number of eligible patients needed.

The minimal number of CKD patients needed for reliable comparison n_{min} is calculated as follows:

$$n_{min} = \frac{n_{tot} \cdot n_n}{n_i}$$

n_{tot} represents the total number of patients in the population, in our case 4,706.

n_n represents the needed number of eligible patients for reliable calculation of the indicator *i*.

n_i represents the number of eligible patients for indicator *i* in the population.

File S3.2: Reasons for discarding indicators during the RAM

Eight prescribing quality indicators (PQIs) were discarded during the consensus meeting of the RAND/UCLA Appropriateness Method. The indicator focusing on the preference of angiotensin-converting-enzyme inhibitor/angiotensin-II-receptor-blockers for hypertension (Table 3.1, PQI I) was discarded because the experts decided that this preference is mainly relevant when albuminuria is present. This aspect was covered in indicators 2 and 3. One of the discarded indicators measuring medication need for mineral and bone disorder focused on starting medication treatment (Table 3.1, PQI II). Given the condition that the PQIs should be defined with routinely collected data, the experts decided that it was not possible to define start of treatment appropriately. The other indicator measuring medication need for mineral and bone disorder was discarded because the experts could not agree on the information needed to assess whether prescribing of vitamin D is indicated (Table 3.1, PQI III). The main reason for discarding all three indicators measuring medication need for anaemia (Table 3.1, PQIs IV, V, VI) was that anaemia is not a specific disorder for patients with chronic kidney disease. The medication safety indicator focusing on adequate monitoring of potassium levels when needed (Table 3.1, PQI VII) was discarded, since it was not possible to define the moment and the frequency of monitoring with routinely collected data. The indicator focusing on prescribing a fixed-combination pill to enhance treatment adherence (Table 3.1, PQI VIII) was discarded because there may be several reasons why patients do not receive such fixed combinations.

Table S3.1: Operationalization final list of prescribing indicators

Overall	**Operationalization**
Age	Determined on 1 January 2012
Gender	Determined on 1 January 2012
eGFR	CKD-EPI formula using last serum creatinine measurement in 2012
CKD stage 3	Last eGFR ≥30 and <60 ml/min/1.73m^2
CKD stage 4	Last eGFR ≥15 and <30 ml/min/1.73m^2
CKD stage 5	Last eGFR <15 ml/min/1.73m^2
Renal replacement therapy	Dialysis in 2012 or kidney transplantation ever
Indicators	**Operationalization**
Treatment of hypertension	
1. The percentage of patients between 18 and 80 years with CKD stages 4-5 and hypertension that is prescribed antihypertensives unless undesirable because of low diastolic blood pressure	· Hypertension: o systolic blood pressure >140 mmHg at last measurement in 2012 and/or o diagnosis code for hypertension K86/87 (ICPC) and/or o ≥1 prescription for antihypertensives in 2012 · Antihypertensives: ATC codes C02, C03, C07, C08, C09 or combinations (as in C10BX) during the last four months in 2012 · Low diastolic blood pressure: <70 mmHg at last measurement in 2012

A

Table S3.1: Operationalization final list of prescribing indicators (continued)

Overall	Operationalization
2a. The percentage of patients between 18 and 80 years with CKD stages 3-5 and macro-albuminuria treated with multiple antihypertensives that is prescribed a combination of an ACE-i or ARB and a diuretic	· Macro-albuminuria: ACR>30 mg/mmol at last measurement in 2012 · Multiple antihypertensives: ≥1 prescription for at least 2 different classes (diuretics, beta blocking agents, calcium channel blockers, RAAS inhibitors, other antihypertensives) during the last four months in 2012 · ACE-i/ARB: ATC codes C09A, C09B, C09C, C09D or combinations (as in C10BX) · Diuretic: ATC codes C03A, C03C, C03BA, C03E
2b. The percentage of patients between 18 and 80 years with CKD stages 3-5, micro-albuminuria and diabetes treated with multiple antihypertensives that is prescribed a combination of an ACE-i or ARB and a diuretic	· Diabetes: diagnosis code for diabetes T90 (ICPC) · Micro-albuminuria: ACR 3-30 mg/mmol at last measurement in 2012 · Multiple antihypertensives: ≥1 prescription for at least 2 different classes (diuretics, beta blocking agents, calcium channel blockers, RAAS inhibitors, other antihypertensives) during the last four months in 2012 · ACE-i/ARB: ATC codes C09A, C09B, C09C, C09D or combinations (as in C10BX) · Diuretic: ATC codes C03A, C03C, C03BA, C03E
Treatment of albuminuria	
3a. The percentage of patients between 18 and 80 years with CKD stages 3-5 and macro-albuminuria that is prescribed an ACE-i or ARB	· Macro-albuminuria: ACR>30 mg/mmol at last measurement in 2012 · ACE-i/ARB: ATC codes C09A, C09B, C09C, C09D or combinations (as in C10BX) during the last four months of 2012
3b. The percentage of patients between 18 and 80 years with CKD stages 3-5, micro-albuminuria and diabetes that is prescribed an ACE-i or ARB	· Diabetes: diagnosis code for diabetes T90 (ICPC) · Micro-albuminuria: ACR 3-30 mg/mmol at last measurement in 2012 · ACE-i/ARB: ATC codes C09A, C09B, C09C, C09D or combinations (as in C10BX) during the last four months of 2012
Prescription of statins	
4. The percentage of patients between 50 and 65 years with CKD stages 3-5 that is prescribed a statin	· Statin: ATC codes C10AA or combination (as in C10BA, C10BX) during last four months of 2012
Treatment of MBD	
5. The percentage of patients between 18 and 80 years with CKD stages 3-5 and an elevated phosphate level that is prescribed a phosphate binder	· Elevated phosphate level: o Phosphate level: >1.49 mmol/l at last measurement in 2012 and/or o ≥1 prescription for phosphate binder during last four months of 2012 · Phosphate binder: ATC codes A12AA04, A12AA12, V03AE02, V03AE03, V03AE04, A02AB01

Table S3.1: Operationalization final list of prescribing indicators (continued)

Overall	Operationalization
6. The percentage of patients between 18 and 80 with CKD stages 3-5 treated with phosphate binders and with an elevated calcium level that is prescribed a non-calcium-containing phosphate binder	· Elevated calcium level: >2.54 mmol/l at last measurement in 2012 · Phosphate binder: ATC codes A12AA04, A12AA12, V03AE02, V03AE03, V03AE04, A02AB01 during last four months of 2012 · Non-calcium containing phosphate binder: ATC codes V03AE02, V03AE03, A02AB01 during last four months of 2012
7. The percentage of patients between 18 and 80 with CKD stages 3-5 treated with phosphate binders and with a low calcium level that is prescribed a calcium-containing phosphate binder	· Low calcium level: <2.10 mmol/l at last measurement in 2012 · Phosphate binder: ATC codes A12AA04, A12AA12, V03AE02, V03AE03, V03AE04, A02AB01 during last four months of 2012 · Calcium containing phosphate binder: ATC codes A12AA04, A12AA12, V03AE04 during last four months of 2012
Medication safety	
8. The percentage of patients 18 years or older with CKD stages 3-5 treated with RAAS inhibitors that is prescribed at least two RAAS inhibitors simultaneously (dual RAAS blockade)	· RAAS inhibitors simultaneously: at least 2 of the ATC codes C09A, C09B, C09C, C09D, C09X or combination (as in C10BX) during last four months 2012
9. The percentage of patients 18 years or older with CKD stages 3-5 and an elevated calcium level that is prescribed active vitamin D	· Elevated calcium level: >2.54 mmol/l at last measurement in 2012 · Active vitamin D: ATC codes A11CC02, A11CC03, A11CC04, H05BX02 during last four months of 2012
10. The percentage of patients 18 years or older with CKD stages 3-5 and an haemoglobin level above target that is prescribed an ESA	· Haemoglobin level: ≥7,5 mmol/l at last measurement in 2012 · ESA: ATC codes B03XA01,B03XA02 during last four months of 2012
11. The percentage of patients 18 years or older with eGFR <30ml/min/1.73m^2 that is prescribed an NSAID	· NSAID: ATC codes M01A, M01BA and B01AC06, B01AC08, B01AC30, B01AC56, N02BA01, N02BA15, N02BA51, N02BA65 in dose >160 mg/day during last four months of 2012
12. The percentage of patients 18 years or older with eGFR <30 ml/min/1.73m^2 and diabetes that is prescribed metformin	· Diabetes: diagnosis code for diabetes T90 (ICPC) · Metformine: ATC codes A10BA02 or combination (as in A10BD) during last four months of 2012
13. The percentage of patients 18 years or older with eGFR <50 ml/min/1.73m^2 treated with digoxin that is prescribed high dose digoxin	· Digoxin: ATC code C01AA05 · High dose digoxin: ATC code C01AA05 in dose >0.125 mg/day during last four months of 2012

A

Table S3.1: Operationalization final list of prescribing indicators (continued)

Overall	Operationalization
14. The percentage of patients 18 years or older with CKD stages 3-5 and that is prescribed a combination of NSAIDs, RAAS inhibitors and diuretics	· Combination of NSAIDs, RAAS inhibitors and diuretics during the last four months of 2012 o NSAIDs: ATC codes M01A, M01BA and B01AC06, B01AC08, B01AC30, B01AC56, N02BA01, N02BA15, N02BA51, N02BA65 in dose > 160 mg/day o RAAS inhibitors: ATC codes C09 and combinations (as in C10BX) o Diuretics: ATC codes C03

eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CKD: chronic kidney disease; ICPC: International Classification of Primary Care; ATC: Anatomical Therapeutic Chemical Classification System; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; ACR: albumin/creatinine ratio; RAAS: renin-angiotensin-aldosterone system; MBD: mineral and bone disease; ESA: erythropoiesis-stimulating agent; NSAID: non-steroidal anti-inflammatory drug, including salicylic acid and derivates.

Appendix 3: Supplemental data chapter 4

Table S4.1: Baseline characteristics per location

	Clinic A (n=569)		Clinic B (n=845)		Clinic C (n=1,718)	
	N (%)	**Mean (±SD)**	**N (%)**	**Mean (±SD)**	**N (%)**	**Mean (±SD)**
Age (years)	569 (100)	63.4 (±14.6)	845 (100)	65.0 (±15.3)	1,718 (100)	70.5 (±12.6)
< 50 years	98 (17.2)		134 (15.9)		131 (7.6)	
50-80 years	397 (69.8)		581 (68.8)		1,171 (68.2)	
≥ 80 years	74 (13.0)		130 (15.4)		416 (24.2)	
Gender (males)	323 (56.8)		446 (52.8)		969 (56.4)	
Diabetes (yes)	145 (25.5)		164 (19.4)		176 (10.2)	
eGFR (MDRD) ml/min	569 (100)	28.4 (±14.2)	845 (100)	35.9 (±14.1)	1,718 (100)	36.5 (±13.1)
Stage 3a	92 (16.2)		255 (30.2)		496 (28.9)	
Stage 3b	166 (29.2)		295 (34.9)		664 (38.7)	
Stage 4	183 (32.2)		219 (25.9)		460 (26.8)	
Stage 5	128 (22.5)		76 (9.0)		98 (5.7)	
SBP (mmHg)	552 (97.0)	131.7 (±18.6)	470 (55.6)	133.4 (±20.7)	1,489 (86.7)	131.7 (±18.2)
Elevated SBP (>140 mmHg)	137 (24.1)	156.2 (±12.7)	143 (16.9)	158.0 (±13.3)	420 (24.4)	154.0 (±11.8)
DBP (mmHg)	552 (97.0)	72.0 (±12.4)	470 (55.6)	76.0 (±10.7)	1,489 (86.7)	76.0 (±10.7)
Low DBP (<70 mmHg)	202 (35.5)	59.4 (±6.9)	100 (11.8)	61.7 (±4.4)	402 (23.4)	62.6 (±5.2)
Total protein (g/24h urine)	513 (90.2)	0.4 [0.1-1.2][a]	244 (28.9)	0.9 [0.3-2.1][a]	557 (32.4)	0.3 [0.1-0.9][a]
Total protein (g/l urine)	515 (90.5)	0.2 [0.1-0.7][a]	574 (67.9)	0.3 [0.1-0.7][a]	1,239 (72.1)	0.2 [0.1-0.4][a]
Proteinuria (>0.5 g/24h or L urine)	215 (37.8)		238 (28.2)		357 (20.8)	
Phosphate (mmol/l)	544 (95.6)	1.20 (±0.33)	623 (73.7)	1.10 (±0.32)	1,439 (83.8)	1.02 (±0.24)
Elevated phosphate (>1.49 mmol/l)	78 (13.7)	1.79 (±0.33)	49 (5.8)	1.87 (±0.40)	45 (2.6)	1.73 (±0.29)
Calcium (mmol/l)	546 (96.0)	2.35 (±0.17)	663 (78.5)	2.34 (±0.14)	1,525 (88.8)	2.37 (±0.12)

A

Table S4.1: Baseline characteristics per location (continued)

	Clinic A (n=569)		Clinic B (n=845)		Clinic C (n=1,718)	
	N (%)	**Mean (±SD)**	**N (%)**	**Mean (±SD)**	**N (%)**	**Mean (±SD)**
Elevated Calcium (>2.54 mmol/l)	35 (6.2)	2.62 (±0.06)	28 (3.3)	2.62 (±0.06)	100 (5.8)	2.62 (±0.09)
Haemoglobin level (mmol/l)	565 (99.3)	7.75 (±1.09)	808 (95.6)	8.0 (±1.2)	1,651 (96.1)	8.1 (±1.1)
Low haemoglobin level (<7.5 mmol/l)	222 (39.0)	6.7 (±0.6)	253 (29.9)	6.7 (±0.6)	458 (26.7)	6.8 (±0.6)

eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Clinic A and B: university nephrology outpatient clinics; clinic C: non-university nephrology outpatient clinic.

[a] Median with interquartile range.

Table S4.2: Baseline table per CKD stage per location

	Clinic A (N=92)		Clinic B (N=255)		Clinic C (N=496)	
CKD stage 3a	**N (%)**	**Mean (±SD)**	**N (%)**	**Mean (±SD)**	**N (%)**	**Mean (±SD)**
Age (years)	92 (100)	56.8 (±13.5)	255 (100)	60.5 (±14.9)	496 (100)	65.6 (±13.4)
< 50 years	26 (28.3)		56 (22.0)		69 (13.9)	
50-80 years	62 (67.4)		182 (71.4)		360 (72.6)	
≥ 80 years	4 (4.4)		17 (6.7)		67 (13.5)	
Gender (males)	46 (50.0)		135 (52.9)		275 (55.4)	
Diabetes (yes)	14 (15.2)		39 (15.3)		43 (8.7)	
eGFR (MDRD) ml/min	92 (100)	51.1 (±4.2)	255 (100)	52.4 (±4.2)	496 (100)	52.3 (±4.4)
SBP (mmHg)	91 (98.9)	126.3 (±17.4)	122 (47.8)	128.5 (±18.8)	388 (78.2)	130.4 (±16.7)
Elevated SBP (>140 mmHg)	12 (13.0)	157.1 (±15.7)	23 (9.0)	157.4 (±12.9)	84 (16.9)	154.5 (±11.7)
DBP (mmHg)	91 (98.9)	73.4 (±12.5)	122 (47.8)	76.0 (±10.5)	388 (78.2)	77.6 (±10.0)
Low DBP (<70 mmHg)	31 (33.7)	59.8 (±6.1)	22 (8.6)	61.3 (±4.4)	77 (15.5)	63.2 (±5.2)
Total protein (g/24h urine)	84 (91.3)	0.2 [0.1-1.0][a]	62 (24.3)	0.5 [0.3-1.3][a]	132 (26.6)	0.2 [0.1-0.5][a]
Total protein (g/l urine)	84 (91.3)	0.1 [0.1-0.4][a]	165 (65.7)	0.1 [0.0-0.4][a]	303 (61.1)	0.1 [0.1-0.3][a]
Proteinuria (>0.5 g/24h or L urine)	29 (31.5)		52 (20.4)		59 (11.9)	
Phosphate (mmol/l)	83 (90.2)	1.02 (±0.20)	139 (54.5)	0.98 (±0.22)	317 (63.9)	0.94 (±0.19)
Elevated phosphate (>1.49 mmol/l)	0 (0.0)	-	2 (0.8)	1.72 (±0.30)	1 (0.2)	1.63 (-)
Calcium (mmol/l)	84 (91.3)	2.38 (±0.14)	159 (62.4)	2.37 (±0.11)	373 (75.2)	2.38 (±0.11)
Elevated Calcium (>2.54 mmol/l)	6 (6.5)	2.60 (±0.05)	7 (2.7)	2.62 (±0.06)	27 (5.4)	2.62 (±0.08)
Haemoglobin level (mmol/l)	90 (97.8)	8.4 (±1.2)	231 (90.6)	8.6 (±1.0)	450 (90.7)	8.4 (±1.0)
Low haemoglobin level (<7.5 mmol/l)	15 (16.3)	6.6 (±0.5)	29 (11.4)	6.8 (±0.6)	69 (13.9)	6.8 (±0.6)

A

Table S4.2: Baseline table per CKD stage per location (continued)

	Clinic A (N=166)		Clinic B (N=295)		Clinic C (N=664)	
CKD stage 3b	**N (%)**	**Mean (±SD)**	**N (%)**	**Mean (±SD)**	**N (%)**	**Mean (±SD)**
Age	166 (100)	63.4 (±14.3)	295 (100)	66.9 (±14.8)	664 (100)	71.2 (±11.5)
< 50 years	33 (19.9)		40 (13.6)		40 (6.0)	
50-80 years	115 (69.3)		200 (67.8)		478 (72.0)	
≥ 80 years	18 (10.8)		55 (18.6)		146 (22.0)	
Gender (males)	98 (59.0)		147 (49.8)		369 (55.6)	
Diabetes (yes)	44 (26.5)		54 (18.3)		68 (10.2)	
eGFR (MDRD) ml/min	166 (100)	36.4 (±4.4)	295 (100)	37.6 (±4.1)	664 (100)	37.4 (±4.2)
SBP (mmHg)	163 (98.2)	129.6 (±17.0)	160 (54.2)	131.6 (±21.0)	587 (88.4)	130.7 (±18.3)
Elevated SBP (>140 mmHg)	33 (19.9)	153.8 (±14.2)	49 (16.6)	156.6 (±12.9)	157 (23.4)	153.7 (±11.9)
DBP (mmHg)	163 (98.2)	72.4 (±12.4)	160 (54.2)	75.5 (±10.3)	587 (88.4)	75.4 (±11.1)
Low DBP (<70 mmHg)	61 (36.7)	60.2 (±6.6)	35 (11.9)	61.8 (±4.2)	186 (28.0)	62.8 (±5.0)
Total protein (g/24h urine)	148 (89.2)	0.2 [0.1-0.6][a]	67 (22.7)	0.7 [0.2-2.0][a]	211 (31.8)	0.2 [0.1-0.7][a]
Total protein (g/l urine)	150 (90.4)	0.2 [0.1-0.4][a]	190 (64.4)	0.2 [0.1-0.5][a]	501 (75.5)	0.2 [0.1-0.4][a]
Proteinuria (>0.5 g/24h or L urine)	39 (23.5)		63 (21.4)		122 (18.4)	
Phosphate (mmol/l)	160 (96.4)	1.04 (±0.21)	213 (72.2)	1.02 (±0.22)	586 (88.3)	0.98 (±0.19)
Elevated phosphate (>1.49 mmol/l)	5 (3.0)	1.58 (±0.04)	6 (2.0)	1.80 (±0.28)	6 (0.9)	1.57 (±0.08)
Calcium (mmol/l)	160 (96.4)	2.37 (±0.15)	231 (78.3)	2.34 (±0.12)	607 (91.4)	2.37 (±0.13)
Elevated Calcium (>2.54 mmol/l)	10 (6.0)	2.62 (±0.06)	7 (2.4)	2.61 (±0.06)	44 (6.6)	2.63 (±0.10)
Haemoglobin level (mmol/l)	166 (100)	8.1 (±1.0)	284 (96.3)	8.1 (±1.1)	645 (97.1)	8.2 (±1.0)
Low haemoglobin level (<7.5 mmol/l)	37 (22.2)	6.9 (±0.5)	81 (27.5)	6.8 (±0.5)	146 (22.0)	6.8 (±0.5)

Table S4.2: Baseline table per CKD stage per location (continued)

	Clinic A (N=183)		Clinic B (N=219)		Clinic C (N=460)	
CKD stage 4	**N (%)**	**Mean (±SD)**	**N (%)**	**Mean (±SD)**	**N (%)**	**Mean (±SD)**
Age	183 (100)	65.3 (±14.6)	219 (100)	67.4 (±15.2)	460 (100)	73.4 (±11.8)
< 50 years	24 (13.1)		26 (11.9)		20 (4.4)	
50-80 years	126 (68.9)		149 (68.0)		281 (61.1)	
≥ 80 years	33 (18.0)		44 (20.1)		159 (34.6)	
Gender (males)	98 (53.6)		119 (54.3)		271 (58.9)	
Diabetes (yes)	55 (30.1)		58 (26.5)		52 (11.3)	
eGFR (MDRD) ml/min	183 (100)	22.3 (±4.2)	219 (100)	23.0 (±4.3)	460 (100)	23.4 (±4.2)
SBP (mmHg)	176 (96.2)	132.0 (±19.4)	140 (63.9)	136.8 (±21.0)	419 (91.1)	132.6 (±18.7)
Elevated SBP (>140 mmHg)	48 (26.2)	156.8 (±11.4)	50 (22.8)	159.1 (±13.8)	135 (29.3)	153.5 (±11.5)
DBP (mmHg)	176 (96.2)	71.6 (±12.8)	140 (63.9)	75.1 (±10.9)	419 (91.1)	75.7 (±10.3)
Low DBP (<70 mmHg)	66 (36.1)	59.0 (±7.6)	38 (17.4)	61.7 (±4.7)	110 (23.9)	62.6 (±5.1)
Total protein (g/24h urine)	163 (89.1)	0.4 [0.1-1.0][a]	75 (34.2)	0.9 [0.3-2.3][a]	165 (35.9)	0.4 [0.2-1.3][a]
Total protein (g/l urine)	163 (89.1)	0.2 [0.1-0.6][a]	162 (74.0)	0.3 [0.2-0.8][a]	362 (78.7)	0.2 [0.1-0.6][a]
Proteinuria (>0.5 g/24h or L urine)	63 (34.4)		77 (35.2)		128 (27.8)	
Phosphate (mmol/l)	176 (96.2)	1.18 (±0.23)	200 (91.3)	1.14 (±0.32)	439 (95.4)	1.05 (±0.2)
Elevated phosphate (>1.49 mmol/l)	16 (8.7)	1.62 (±0.11)	17 (7.8)	1.84 (±0.47)	8 (1.7)	1.66 (±0.11)
Calcium (mmol/l)	176 (96.2)	2.35 (±0.20)	199 (90.9)	2.34 (±0.16)	447 (97.2)	2.36 (±0.12)
Elevated Calcium (>2.54 mmol/l)	13 (7.1)	2.61 (±0.07)	9 (4.1)	2.65 (±0.07)	24 (5.2)	2.62 (±0.06)
Haemoglobin level (mmol/l)	182 (99.5)	7.6 (±1.0)	217 (99.1)	7.7 (±1.2)	458 (99.6)	7.8 (±1.0)
Low haemoglobin level (<7.5 mmol/l)	82 (44.8)	6.7 (±0.7)	89 (40.6)	6.6 (±0.6)	175 (38.0)	6.7 (±0.6)

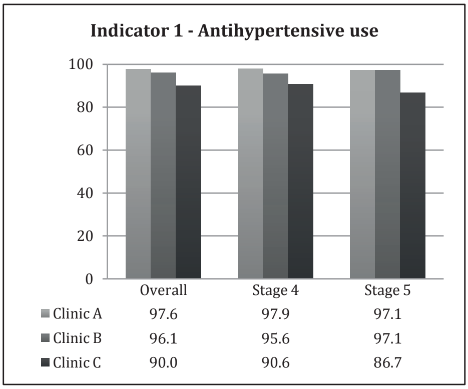
A

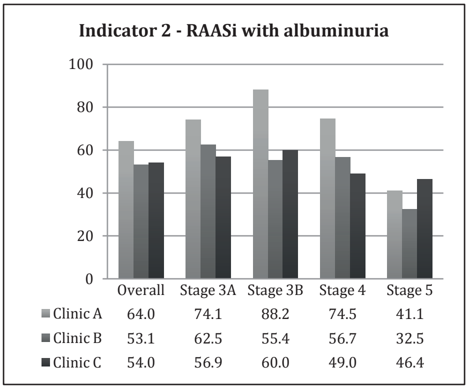
Table S4.2: Baseline table per CKD stage per location (continued)

	Clinic A (N=128)		Clinic B (N=76)		Clinic (N=98)	
CKD stage 5	**N (%)**	**Mean (±SD)**	**N (%)**	**Mean (±SD)**	**N (%)**	**Mean (±SD)**
Age	128 (100)	65.5 (±14.7)	76 (100)	65.5 (±15.9)	98 (100)	76.9 (±10.6)
< 50 years	15 (11.7)		12 (15.8)		2 (2.0)	
50-80 years	94 (73.4)		40 (65.8)		52 (53.1)	
≥ 80 years	19 (14.8)		14 (18.4)		44 (44.9)	
Gender (males)	81 (63.3)		45 (59.2)		54 (55.1)	
Diabetes (yes)	32 (25.0)		13 (17.1)		13 (13.3)	
eGFR (MDRD) ml/min	128 (100)	10.5 (±2.6)	76 (100)	11.2 (±2.4)	98 (100)	11.9 (±2.6)
SBP (mmHg)	122 (95.3)	137.9 (±18.6)	48 (63.2)	142.1 (±19.8)	95 (96.9)	139.2 (±19.7)
Elevated SBP (>140 mmHg)	44 (34.4)	157.1 (±12.2)	21 (27.6)	159.6 (±14.2)	44 (44.9)	155.9 (±12.2)
DBP (mmHg)	122 (95.3)	71.1 (±11.6)	48 (63.2)	80.6 (±11.4)	95 (96.9)	74.4 (±11.9)
Low DBP (<70 mmHg)	44 (34.4)	58.5 (±6.7)	5 (6.6)	62.2 (±4.1)	29 (29.6)	60.2 (±6.4)
Total protein (g/24h urine)	118 (92.2)	1.3 [0.5-2.7][a]	40 (52.6)	1.9 [0.9-4.1][a]	49 (50.0)	1.0 [0.4-2.6][a]
Total protein (g/l urine)	118 (92.2)	0.7 [0.3-1.4][a]	57 (75.0)	1.4 [0.5-2.4][a]	73 (74.5)	0.6 [0.3-1.1][a]
Proteinuria (>0.5 g/24h or L urine)	84 (65.6)		57 (60.5)		48 (49.0)	
Phosphate (mmol/l)	125 (97.7)	1.55 (±0.39)	71 (93.4)	1.47 (±0.42)	97 (99.0)	1.39 (±0.36)
Elevated phosphate (>1.49 mmol/l)	57 (44.5)	1.86 (±0.36)	24 (31.6)	1.92 (±0.39)	30 (30.6)	1.79 (±0.34)
Calcium (mmol/l)	126 (98.4)	2.31 (±0.16)	74 (97.4)	2.27 (±0.19)	98 (100)	2.32 (±0.14)
Elevated Calcium (>2.54 mmol/l)	13 (10.2)	2.65 (±0.07)	5 (6.6)	2.63 (±0.08)	5 (5.1)	2.66 (±0.11)
Haemoglobin level (mmol/l)	127 (99.2)	7.0 (±0.8)	76 (100)	7.0 (±1.2)	98 (100)	7.0 (±0.9)
Low haemoglobin level (<7.5 mmol/l)	88 (68.8)	6.6 (±0.5)	54 (71.1)	6.4 (±0.8)	68 (69.4)	6.6 (±0.7)

CKD: chronic kidney disease; SD: standard deviation; eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; SBP: systolic blood pressure; DBP: diastolic blood pressure.
Clinic A and B: university nephrology outpatient clinics; clinic C: non-university nephrology outpatient clinic.
[a] Median with interquartile range.

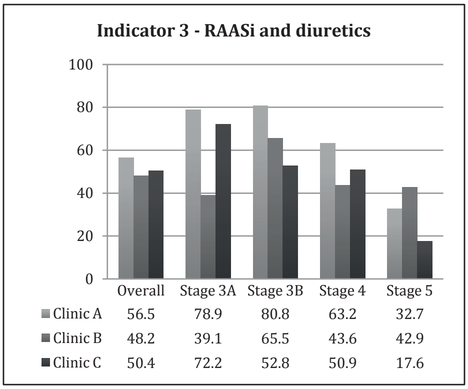
Table S4.3: Differences between outpatient clinics per indicator stratified for CKD stage

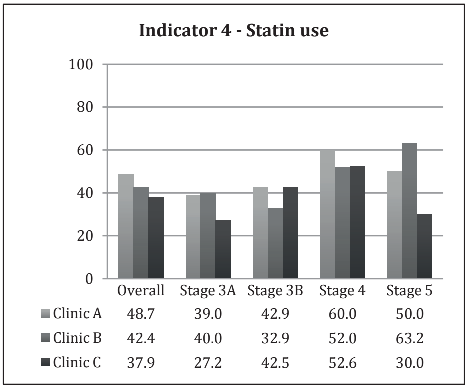




Overall	p-value χ^2	*Overall*	p-value χ^2
Clinic A vs. Clinic B	0.316	Clinic A vs. Clinic B	0.030
Clinic A vs. Clinic C	**0.003**	Clinic A vs. Clinic C	**0.003**
Clinic B vs. Clinic C	0.095	Clinic B vs. Clinic C	0.503
CKD stage 4		*CKD stage 3a*	
Clinic A vs. Clinic B	0.406†	Clinic A vs. Clinic B	0.190
Clinic A vs. Clinic C	**0.011**	Clinic A vs. Clinic C	0.095
Clinic B vs. Clinic C	0.196	Clinic B vs. Clinic C	0.675
CKD stage 5		*CKD stage 3b*	
Clinic A vs. Clinic B	1.000†	Clinic A vs. Clinic B	**0.002**
Clinic A vs. Clinic C	0.103†	Clinic A vs. Clinic C	**0.001**
Clinic B vs. Clinic C	0.306†	Clinic B vs. Clinic C	0.819
		CKD stage 4	
		Clinic A vs. Clinic B	0.089
		Clinic A vs. Clinic C	**0.001**
		Clinic B vs. Clinic C	0.117
		CKD stage 5	
		Clinic A vs. Clinic B	0.209
		Clinic A vs. Clinic C	0.243
		Clinic B vs. Clinic C	0.923

Table S4.3: Differences between outpatient clinics per indicator stratified for CKD stage (continued)



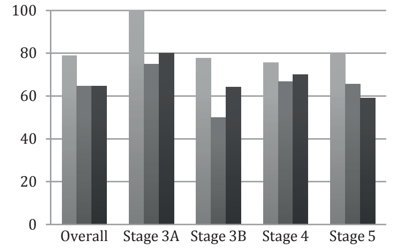


Overall	p-value χ^2	*Overall*	p-value χ^2
Clinic A vs. Clinic B	0.184	Clinic A vs. Clinic B	0.205
Clinic A vs. Clinic C	0.081	Clinic A vs. Clinic C	**0.015**
Clinic B vs. Clinic C	0.786	Clinic B vs. Clinic C	0.277
CKD stage 3a		*CKD stage 3a*	
Clinic A vs. Clinic B	**0.014**	Clinic A vs. Clinic B	0.916
Clinic A vs. Clinic C	1.000	Clinic A vs. Clinic C	0.140
Clinic B vs. Clinic C	**0.014**	Clinic B vs. Clinic C	0.042
CKD stage 3b		*CKD stage 3b*	
Clinic A vs. Clinic B	0.068	Clinic A vs. Clinic B	0.266
Clinic A vs. Clinic C	**0.002**	Clinic A vs. Clinic C	0.966
Clinic B vs. Clinic C	0.235	Clinic B vs. Clinic C	0.189
CKD stage 4		*CKD stage 4*	
Clinic A vs. Clinic B	0.245	Clinic A vs. Clinic B	0.409
Clinic A vs. Clinic C	0.337	Clinic A vs. Clinic C	0.395
Clinic B vs. Clinic C	0.766	Clinic B vs. Clinic C	0.950
CKD stage 5		*CKD stage 5*	
Clinic A vs. Clinic B	0.586	Clinic A vs. Clinic B	0.340
Clinic A vs. Clinic C	0.033	Clinic A vs. Clinic C	0.309†
Clinic B vs. Clinic C	0.021	Clinic B vs. Clinic C	0.128†

A

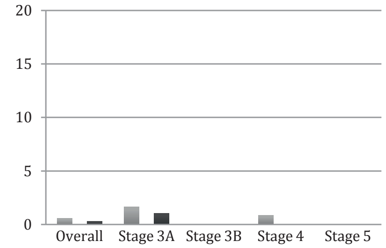
Table S4.3: Differences between outpatient clinics per indicator stratified for CKD stage (continued)

Indicator 5 - Phosphate binder use



	Overall	Stage 3A	Stage 3B	Stage 4	Stage 5
Clinic A	78.9	100.0	77.8	75.6	80.0
Clinic B	64.6	75.0	50.0	66.7	65.5
Clinic C	64.7	80.0	64.3	70.0	59.1

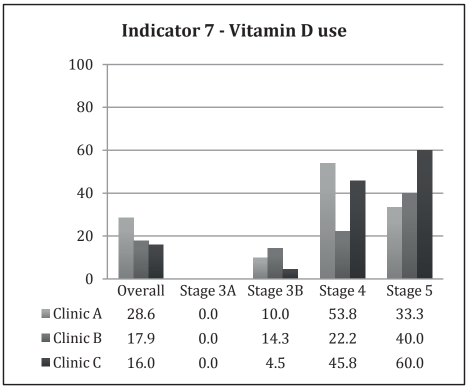
Indicator 6 - Dual RAAS blockade

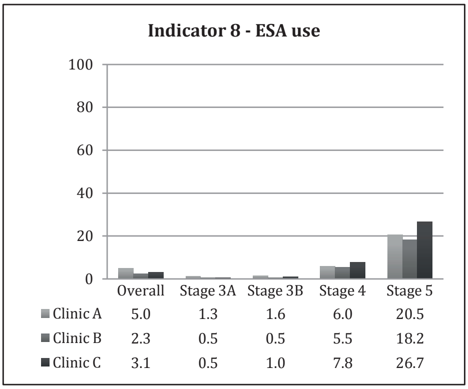


	Overall	Stage 3A	Stage 3B	Stage 4	Stage 5
Clinic A	0.6	1.7	0.0	0.9	0.0
Clinic B	0.0	0.0	0.0	0.0	0.0
Clinic C	0.3	1.0	0.0	0.0	0.0

Overall	p-value χ^2	*Overall*	p-value χ^2
Clinic A vs. Clinic B	**0.016**	Clinic A vs. Clinic B	0.218†
Clinic A vs. Clinic C	0.030	Clinic A vs. Clinic C	0.612†
Clinic B vs. Clinic C	0.849	Clinic B vs. Clinic C	0.530†
CKD stage 3a		*CKD stage 3a*	
Clinic A vs. Clinic B	1.000†	Clinic A vs. Clinic B	0.323†
Clinic A vs. Clinic C	1.000†	Clinic A vs. Clinic C	0.558†
Clinic B vs. Clinic C	1.000†	Clinic B vs. Clinic C	0.521†
CKD stage 3b		*CKD stage 3b*	
Clinic A vs. Clinic B	0.650†	Clinic A vs. Clinic B	No prescriptions
Clinic A vs. Clinic C	1.000†	Clinic A vs. Clinic C	No prescriptions
Clinic B vs. Clinic C	0.692†	Clinic B vs. Clinic C	No prescriptions
CKD stage 4		*CKD stage 4*	
Clinic A vs. Clinic B	0.191	Clinic A vs. Clinic B	1.000†
Clinic A vs. Clinic C	0.548	Clinic A vs. Clinic C	0.391†
Clinic B vs. Clinic C	0.620	Clinic B vs. Clinic C	No prescriptions
CKD stage 5		*CKD stage 5*	
Clinic A vs. Clinic B	0.067	Clinic A vs. Clinic B	No prescriptions
Clinic A vs. Clinic C	**0.013**	Clinic A vs. Clinic C	No prescriptions
Clinic B vs. Clinic C	0.575	Clinic B vs. Clinic C	No prescriptions

Table S4.3: Differences between outpatient clinics per indicator stratified for CKD stage (continued)

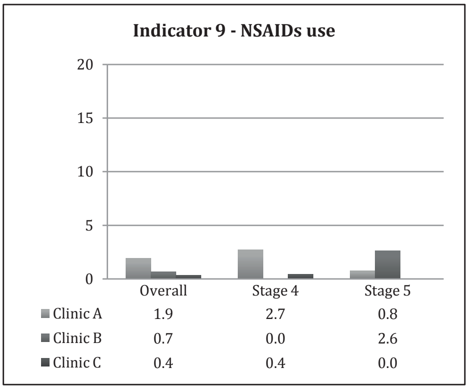


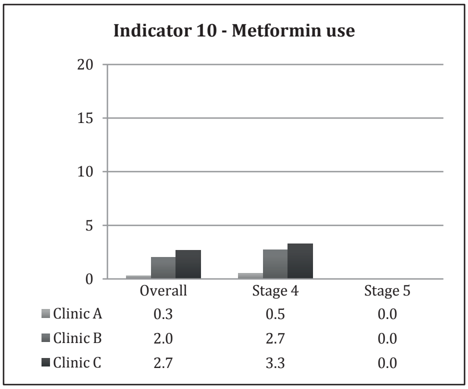


Overall	p-value χ^2	*Overall*	p-value χ^2
Clinic A vs. Clinic B	0.321	Clinic A vs. Clinic B	0.034
Clinic A vs. Clinic C	0.105	Clinic A vs. Clinic C	0.100
Clinic B vs. Clinic C	0.779†	Clinic B vs. Clinic C	0.375
CKD stage 3a		*CKD stage 3a*	
Clinic A vs. Clinic B	No prescriptions	Clinic A vs. Clinic B	0.469†
Clinic A vs. Clinic C	No prescriptions	Clinic A vs. Clinic C	0.417†
Clinic B vs. Clinic C	No prescriptions	Clinic B vs. Clinic C	1.000†
CKD stage 3b		*CKD stage 3b*	
Clinic A vs. Clinic B	1.000†	Clinic A vs. Clinic B	0.562†
Clinic A vs. Clinic C	0.466†	Clinic A vs. Clinic C	0.637†
Clinic B vs. Clinic C	0.364†	Clinic B vs. Clinic C	0.678†
CKD stage 4		*CKD stage 4*	
Clinic A vs. Clinic B	0.203†	Clinic A vs. Clinic B	0.864
Clinic A vs. Clinic C	0.642	Clinic A vs. Clinic C	0.558
Clinic B vs. Clinic C	0.263†	Clinic B vs. Clinic C	0.398
CKD stage 5		*CKD stage 5*	
Clinic A vs. Clinic B	1.000†	Clinic A vs. Clinic B	1.000†
Clinic A vs. Clinic C	0.567†	Clinic A vs. Clinic C	0.548
Clinic B vs. Clinic C	1.000†	Clinic B vs. Clinic C	0.473

A

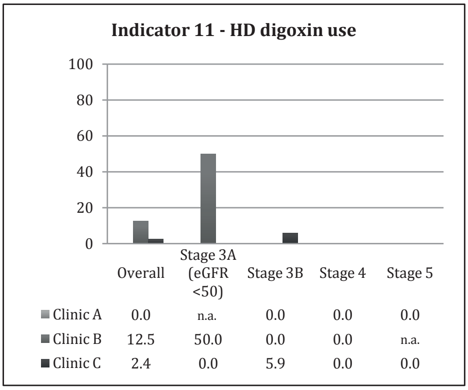
Table S4.3: Differences between outpatient clinics per indicator stratified for CKD stage (continued)

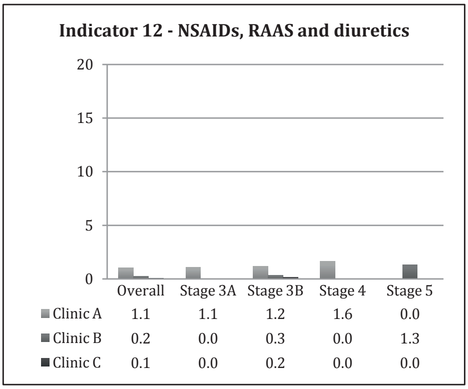




Overall	p-value χ^2	*Overall*	p-value χ^2
Clinic A vs. Clinic B	0.287†	Clinic A vs. Clinic B	0.062
Clinic A vs. Clinic C	0.028†	Clinic A vs. Clinic C	**0.013**
Clinic B vs. Clinic C	0.612†	Clinic B vs. Clinic C	0.558
CKD stage 4		*CKD stage 4*	
Clinic A vs. Clinic B	0.019†	Clinic A vs. Clinic B	0.132†
Clinic A vs. Clinic C	0.022†	Clinic A vs. Clinic C	0.050†
Clinic B vs. Clinic C	1.000†	Clinic B vs. Clinic C	0.714
CKD stage 5		*CKD stage 5*	
Clinic A vs. Clinic B	0.557†	Clinic A vs. Clinic B	No prescriptions
Clinic A vs. Clinic C	1.000†	Clinic A vs. Clinic C	No prescriptions
Clinic B vs. Clinic C	0.189†	Clinic B vs. Clinic C	No prescriptions

Table S4.3: Differences between outpatient clinics per indicator stratified for CKD stage (continued)





Overall	p-value χ^2	*Overall*	p-value χ^2
Clinic A vs. Clinic B	1.000†	Clinic A vs. Clinic B	0.067†
Clinic A vs. Clinic C	1.000†	Clinic A vs. Clinic C	**0.001**†
Clinic B vs. Clinic C	0.202†	Clinic B vs. Clinic C	0.254†
CKD stage 3a		*CKD stage 3a*	
Clinic A vs. Clinic B	No prescriptions	Clinic A vs. Clinic B	0.265†
Clinic A vs. Clinic C	No prescriptions	Clinic A vs. Clinic C	0.156†
Clinic B vs. Clinic C	0.333†	Clinic B vs. Clinic C	No prescriptions
CKD stage 3b		*CKD stage 3b*	
Clinic A vs. Clinic B	No prescriptions	Clinic A vs. Clinic B	0.295†
Clinic A vs. Clinic C	1.000†	Clinic A vs. Clinic C	0.104†
Clinic B vs. Clinic C	1.000†	Clinic B vs. Clinic C	0.521†
CKD stage 4		*CKD stage 4*	
Clinic A vs. Clinic B	No prescriptions	Clinic A vs. Clinic B	0.093†
Clinic A vs. Clinic C	No prescriptions	Clinic A vs. Clinic C	0.023†
Clinic B vs. Clinic C	No prescriptions	Clinic B vs. Clinic C	1.000†
CKD stage 5		*CKD stage 5*	
Clinic A vs. Clinic B	No prescriptions	Clinic A vs. Clinic B	0.373†
Clinic A vs. Clinic C	No prescriptions	Clinic A vs. Clinic C	No prescriptions
Clinic B vs. Clinic C	No prescriptions	Clinic B vs. Clinic C	0.437†

CKD: chronic kidney disease; RAAS: renin-angiotensin-aldosterone system; ESA: erythropoiesis-stimulating agent; NSAID: non-steroidal anti-inflammatory drug.
Clinic A and B: university nephrology outpatient clinics; clinic C: non-university nephrology outpatient clinic.
† Fisher's exact because of <5 expected number of patients in one or more cells.

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Appendix 4: Supplemental data chapter 5

Table S5.1: Results of all rounds of the RAND/UCLA method

List of indicators (*italic* reflects indicators removed during consensus meeting, between brackets reflects the original numbering)	Round 1 Correct reflection of guidelines	Correct definitions A	B	C	D	E
Glucose lowering drugs						
(1A.) The percentage of patients with T2D that reached the target level for HbA_{1c} (≤53 mmol/mol) without glucose lowering drugs	7.5-	9+	8-	9+		
(1B.) The percentage of patients with T2D between 18 and 55 years that reached the target level for HbA_{1c} (≤53 mmol/mol) with glucose lowering drugs	8-	5.5-	8+	9+		
(1C.) The percentage of patients with T2D between 55 and 70 years that reached the target level for HbA_{1c} (≤53 mmol/mol) with glucose lowering drugs	8.5+	6.5-	8+	9+		
1. (2.) The percentage of patients with T2D between 18 and 70 years with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that started with glucose lowering drugs or that reached the HbA_{1c} target level (≤53 mmol/mol)	8+	7+	7.5-	7.5-	9+	
2. (3.) The percentage of patients with T2D between 18 and 70 years treated with monotherapy metformin and with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that is intensified with glucose lowering drugs or that reached the HbA_{1c} target level (≤53 mmol/mol)	8-	8+	6.5-	6.5-	8.5+	9+
3. (4A.) The percentage of patients with T2D between 18 and 70 years treated with two or more non-insulin glucose lowering drugs and with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that started with insulin or that reached the HbA_{1c} target level (≤53 mmol/mol)	8+	9+	8-	7.5-	8.5+	9+
4B. The percentage of patients with T2D 70 years or older and a diabetes duration of less than 10 years treated with two or more non-insulin glucose lowering drugs and with an elevated HbA_{1c} level (>58 mmol/mol) in the previous year, that started with insulin or that reached the HbA_{1c} target level (≤58 mmol/mol)	8+	9+	8+	8+	8.5+	9+
4C. The percentage of patients with T2D 70 years or older and a diabetes duration of 10 or more years treated with two or more non-insulin glucose lowering drugs and with an elevated HbA_{1c} level (>64 mmol/mol) in the previous year, that started with insulin or that reached the HbA_{1c} target level (≤64 mmol/mol)	8+	9+	8+	8+	8.5+	8.5+
4. The percentage of patients with T2D 18 years or older that started with metformin among all starters of oral glucose lowering drugs						

	Consensus meeting	Round 3		
Health gain for patient		Correct reflection of guidelines	Health gain for patient	Necessary aspect
6.5-	Removed			
7+	Removed			
7+	Removed			
7+	· Age restriction to 70 years	9+	8+	7.5+
7+	· Age restriction to 70 years	9+	8+	8+
7.5+	No changes	8.5+	8+	8+
6.5-	Removed			
7+	Removed			
	New	9+	8+	8+

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Table S5.1: Results of all rounds of the RAND/UCLA method (continued)

	Round 1					
		Correct definitions				
List of indicators (*italic* reflects indicators removed during consensus meeting, between brackets reflects the original numbering)	Correct reflection of guidelines	A	B	C	D	E
5. (5.) The percentage of patients with T2D 18 years or older treated with glucose lowering drugs that is prescribed metformin	8+	9+	9+	9+		
6. The percentage of patients with T2D 18 years or older treated with metformin that started with an SU-derivative among all starters of a second non-insulin glucose lowering drugs						
6. (6.) The percentage of patients with T2D 18 years or older treated with two non-insulin glucose lowering drugs that is prescribed a combination of metformin and an SU-derivative	7.5+	9+	9+	9+	9+	
7. (7.) The percentage of patients with T2D 18 years or older that started with gliclazide among all starters of an SU-derivative	8-	9+	9+	9+		
Lipid lowering drugs						
8. (11.) The percentage of patients with T2D between 55 and 80 years that is prescribed a statin	5.5-	8.5+	9+	3-		
9. (12.) The percentage of patients with T2D between 18 and 80 years with an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that started with a statin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)	5.5-	7.5-	3-	9+	9+	
10. (13.) The percentage of patients with T2D between 18 and 80 years treated with simvastatin and with an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that switched to atorvastatin or rosuvastatin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)	8.5+	9+	7+	9+	9+	9+
14. The percentage of patients with T2D that started with simvastatin among all starters with statins	8.5+	9+	9+	8.5+		
Blood pressure lowering drugs						
12A (15A.) The percentage of patients with T2D between 18 and 55 years with an elevated systolic blood pressure (>160 mmHg) in the previous year, that started with antihypertensives or that reached the systolic blood pressure target level (≤160 mmHg)	8+	8.5+	5.5-	9+	9+	
12B. (15B.) The percentage of patients with T2D between 55 and 70 years with an elevated systolic blood pressure (>140 mmHg) in the previous year, that started with antihypertensives or that reached the systolic blood pressure target level (≤140 mmHg)	8+	8.5+	8.5-	9+	9+	

	Consensus meeting	Round 3		
Health gain for patient		Correct reflection of guidelines	Health gain for patient	Necessary aspect
8+	· Old indicator 5 was split in two indicators, one on starters of oral glucose lowering drugs (ind 4) and one on prevalent use of metformin in all users of glucose lowering drug (ind 5)	9+	8.5+	8+
	New	9+	6.5+	7+
5.5-	No changes	9+	7+	7.5+
6.5-	· Changed to starters of a SU-derivative	9+	8+	8+
8.5+	· Age restriction to 55-80 years	8.5+	9+	9+
8+	· Age restriction to younger than 80 years · Removed criteria 'cardiovascular risk'	8.5+	8.5+	8+
7+	· Age restriction to younger than 80 years · Removed criteria 'cardiovascular risk'	8+	7.5+	7.5+
6-	Removed			
8.5+	· Target level of 140 mmHg changed into 160 mmHg	8.5+	9+	9+
9+	· Age restricted to younger than 70 years	8.5+	8+	8.5+

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Table S5.1: Results of all rounds of the RAND/UCLA method (continued)

List of indicators (*italic* reflects indicators removed during consensus meeting, between brackets reflects the original numbering)	Round 1: Correct reflection of guidelines	Correct definitions: A	B	C	D	E
15C. The percentage of patients with T2D 80 years or older with an elevated systolic blood pressure (>160 mmHg) in the previous year, that started with antihypertensives or reached the blood pressure target level (≤160 mmHg)	8+	9+	8.5+	6.5-	9+	
11. The percentage of patients with T2D between 18 and 70 years with an elevated systolic blood pressure (>140 mmHg) in the previous year, that started with antihypertensives or reached the systolic blood pressure target level (≤140 mmHg)						
12. (16.) The percentage of patients with T2D between 18 and 70 years treated with monotherapy antihypertensives and with an elevated systolic blood pressure (>140 mmHg) in the previous year, that is intensified with antihypertensives or that reached the systolic blood pressure target level (≤140 mmHg)	8+	9+	9+	7.5+	9+	
Albuminuria lowering drugs						
13. (18.) The percentage of patients with T2D 18 years or older treated with two or more antihypertensives that is prescribed an ACE-i or ARB	9+	9+	9+	9+		
14. (19.) The percentage of patients with T2D between 18 and 70 years with micro- or macro-albuminuria† in the previous year, that started with an ACE-i or ARB or that returned to normo-albuminuria†	8.5+	7.5+	9+	9+	9+	
15. (20.) The percentage of patients with T2D 18 years or older treated with antihypertensives and with micro- or macro-albuminuria† that is prescribed an ACE-i or ARB	8+	9+	9+	9+	9+	
16. The percentage of patients with T2D 18 years or older that started with an ACE-i among all patients that started with RAAS treatment						
Medication safety						
17. (8.) The percentage of patients with T2D 18 years or older treated with SU-derivatives that is prescribed glibenclamide	9+	9+	9+	9+		
18. (9.) The percentage of patients with T2D 18 years or older with an eGFR <30 ml/min/1.73m^2 that is prescribed metformin	8.5+	9+	9+	8.5+		

	Consensus meeting	**Round 3**		
Health gain for patient		Correct reflection of guidelines	Health gain for patient	Necessary aspect
6.5-	Removed			
	New, combination of 12A en 12B after round 3	8+	8+	8+
8+	· Age restricted to younger than 70 years	8+	8+	8+
7.5+	No changes	9+	8.5+	8.5+
7.5+	Age restriction to younger than 70 years	9+	8.5+	9+
8+	No changes	9+	8.5+	9+
	New	9+	7+	7+
8+	No changes	9+	9+	8.5+
7+	No changes	9+	8+	8.5+

Table S5.1: Results of all rounds of the RAND/UCLA method (continued)

	Round 1					
List of indicators (*italic* reflects indicators removed during consensus meeting, between brackets reflects the original numbering)	Correct reflection of guidelines	Correct definitions A	B	C	D	E
19. The percentage of patients with T2D 80 years or older with a normal HbA_{1c} level (<53 mmol/mol) that is prescribed two or more glucose lowering drugs						
10. The percentage of patients with T2D 18 years or older that is prescribed a combination of pioglitazone and insulin	9+	9+	9+	9+		
17. The percentage of patients with T2D 80 years or older and a systolic blood pressure <150 mmHg that is intensified with antihypertensives	8+	9+	9+	9+		
21. The percentage of patients with T2D 18 years or older with RAAS treatment or diuretics which serum potassium was measured yearly	9+	9+	9+	9+	9+	
20. (22.) The percentage of patients with T2D 18 years or older treated with RAAS inhibitors that is prescribed a combination of an ACE-i and ARB (dual RAAS blockade)	9+	9+	9+			
Vaccination						
23. The percentage of patients with T2D 18 years or older that is vaccinated for the flu	9+	9+	9+			
Therapy adherence						
24. The percentage of patients with T2D 18 years or older that received less than three repeat prescriptions for glucose lowering drugs	6-	9+	9+			
25. The percentage of patients with T2D 18 years or older that received less than three repeat prescriptions for lipid lowering medication	6-	9+	9+			
26. The percentage of patients with T2D 18 years or older that received less than three repeat prescriptions for antihypertensives	6.5-	8.5+	9+			

T2D: type 2 diabetes; HbA_{1c}: glycated haemoglobin; SU-derivative: sulphonylurea derivatives; LDL-cholesterol; low-density lipoprotein-cholesterol; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; RAAS: renin-angiotensin-aldosterone system; eGFR: estimated glomerular filtration rate.

† Micro/macro-albuminuria is defined as an albumin/creatinine ratio ≥2.5 mg/mmol for males and ≥3.5 mg/mmol for females. Normo-albuminurie is defined as an albumin/creatinine ratio <2.5 mg/mmol for males and <3.5 mg/mmol for females.

	Consensus meeting	Round 3		
Health gain for patient		Correct reflection of guidelines	Health gain for patient	Necessary aspect
	New	9+	8.5+	9+
8+	Removed			
8+	Removed			
8+	Removed			
7.5+	· Denominator changed into RAAS treatment (regardless the amount)	9+	9+	9+
6-	Removed			
5-	Removed			
5-	Removed			
4-	Removed			

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Table S5.2: Operational definitions for selected prescribing quality indicators

Overall	**Operationalization**
Age	Determined on 1 January 2012
Gender	Determined on 1 January 2012
T2D	Determined on 1 January 2012: diagnosis code T90 (ICPC)
Indicators	
Glucose lowering drugs	
1. The percentage of patients with T2D between 18 and 70 years with an elevated HbA_{1c} level in the previous year, that started with glucose lowering drugs or that reached the HbA_{1c} target level	· Elevated HbA_{1c}: most recent measurement in previous year (2011) >53 mmol/mol · Target level HbA_{1c}: most recent measurement in current year (2012) ≤53 mmol/mol · Start with glucose lowering drugs: o No prescriptions (ATC codes: A10A, A10B) in (last 4 months of) previous year (2011) and o ≥1 prescription (ATC codes: A10A, A10B) in (last 4 months of) current year (2012)
2. The percentage of patients with T2D between 18 and 70 years treated with monotherapy metformin and with an elevated HbA_{1c} level in the previous year, that is intensified with glucose lowering drugs or that reached the HbA_{1c} target level	· Elevated HbA_{1c}: most recent measurement in previous year (2011) >53 mmol/mol · Target level HbA_{1c}: most recent measurement in current year (2012) ≤53 mmol/mol · Metformin monotherapy: ≥1 prescription (ATC code: A10BA02) in (last 4 months of) previous year (2011) without any prescription for A10A, A10BB, A10BD, A10BF, A10BG, A10BH, A10BX in (last 4 months of) previous year (2011) · Intensified treatment: ≥1 prescriptions (ATC codes: A10A, A10BA02, A10BB, A10BD, A10BF, A10BG, A10BH, A10BX) in (last 4 months of) current year (2012)
3. The percentage of patients with T2D between 18 and 70 years treated with two or more non-insulin glucose lowering drugs and with an elevated HbA_{1c} level in the previous year, that started with insulin or that reached the HbA_{1c} target level	· Elevated HbA_{1c}: most recent measurement in previous year (2011) >53 mmol/mol · Target level HbA_{1c}: most recent measurement in current year (2012) ≤53 mmol/mol · Two or more non-insulin glucose lowering drugs: ≥1 prescription for ≥2 drug classes (ATC codes: A10BA, A10BB, A10BF, A10BG, A10BH, A10BX) or ≥1 prescription for drug class (ATC code: A10BD) in (last 4 months of) previous year (2011) · Start with insulin: o No prescriptions (ATC code: A10A) in (last 4 months of) previous year (2011) and o ≥1 prescription (ATC code: A10A) in (last 4 months of) current year (2012)

Table S5.2: Operational definitions for selected prescribing quality indicators (continued)

Overall	**Operationalization**
4. The percentage of patients with T2D 18 years or older that started with metformin among all starters of oral glucose lowering drugs (exclusion criterion: eGFR <30 ml/min/1.73 m^2)	· Start with metformin: o No prescriptions (ATC code: A10BA02) in (last 4 months of) previous year (2011) and o ≥1 prescription (ATC code: A10BA02) in (last 4 months of) current year (2012) · Start with oral glucose lowering drugs: o No prescriptions (ATC code: A10B) in (last 4 months of) previous year (2011) and o ≥1 oral glucose lowering drug prescriptions (ATC code: A10B) in (last 4 months of) current year (2012) · eGFR <30 ml/min/1.73 m^2 based on CKD-EPI formula using most recent serum creatinine measurement in current year (2012)
5. The percentage of patients with T2D 18 years or older treated with glucose lowering drugs that is prescribed metformin (exclusion criterion: eGFR <30 ml/min/1.73m^2)	· Metformin treatment: ≥1 prescription (ATC codes: A10BA02, A10BD02, A10BD03, A10BD05, A10BD07, C10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD17, A10BD18) in (last 4 months of) current year (2012) · Glucose lowering drugs: ≥1 prescription (ATC codes: A10A, A10B) in (last 4 months of) current year (2012) · eGFR <30 ml/min/1.73 m^2 based on CKD-EPI formula using most recent serum creatinine measurement in current year (2012)
6. The percentage of patients with T2D 18 years or older treated with two non-insulin glucose lowering drugs that is prescribed a combination of metformin and an SU-derivative (exclusion criterion: eGFR <30 ml/min/1.73m^2)	· Metformin treatment: ≥1 prescription (ATC codes: A10BA02, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD17, A10BD18, A10BD20) in (last 4 months of) the current year (2012) · SU-derivate treatment: ≥1 prescription (ATC codes: A10BB, A10BD02, A10BD04, A10BD06) in (last 4 months) of the current year (2012) · Two non-insulin glucose lowering drugs: o ≥1 prescription for 2 drug classes (ATC codes: A10BA, A10BB, A10BF, A10BG, A10BH, A10BX) or o ≥1 prescription for drug class (ATC code: A10BD) in (last 4 months of) current year (2012) · eGFR < 30 ml/min/1.73m^2 based on CKD-EPI formula using most recent serum creatinine measurement in current year (2012)

Table S5.2: Operational definitions for selected prescribing quality indicators (continued)

Overall	**Operationalization**
7. The percentage of patients with T2D 18 years or older that started with gliclazide among all starters of an SU-derivative	· Start SU-derivate: o No prescriptions (ATC codes: A10BB, A10BD02, A10BD04, A10BD06) in (last 4 months of) previous year (2011) and o ≥1 prescription (ATC codes: A10BB, A10BD02, A10BD04, A10BD06) in (last 4 months of) current year (2012) · Gliclazide therapy: ≥1 prescription (ATC code: A10BB09) in (last 4 months of) current year (2012)
Lipid lowering drugs	
8. The percentage of patients with T2D between 55 and 80 years that is prescribed a statin	· Statin treatment: ≥ 1 prescription (ATC code: C10AA) in (last 4 months of) current year (2012)
9. The percentage of patients with T2D between 18 and 80 years with an elevated LDL-cholesterol level in the previous year, that started with a statin or that reached the LDL-cholesterol target level	· Elevated LDL-cholesterol: most recent measurement in previous year (2011) >2.5 mmol/l · Target level LDL-cholesterol: most recent measurement in current year (2012) ≤2.5 mmol/l · Start statin: o No prescriptions (ATC code: C10AA) in (last 4 months of) previous year (2011) and o ≥1 prescription (ATC code: C10AA) in (last 4 months of) current year (2012)
10. The percentage of patients with T2D between 18 and 80 years treated with simvastatin and with an elevated LDL-cholesterol level in the previous year, that switched to atorvastatin or rosuvastatin or that reached the LDL-cholesterol target level	· Elevated LDL-cholesterol: most recent measurement in previous year (2011) >2.5 mmol/l · Target level LDL-cholesterol: most recent measurement in current year (2012) ≤2.5 mmol/l · Simvastatin therapy: ≥1 prescription (ATC codes: C10AA01, C10BA02, C10BA04, C10BX01, C10BX04) in (last 4 months of) previous year (2011) · Atorvastatin therapy: ≥1 prescription (ATC codes: C10AA05. C10BA05, C10BX06, C10BX08) in the last 4 months of current year (2012) · Rosuvastatin therapy: ≥1 prescription (ATC codes: C10AA07, C10BA06, C10BX05, C10BX07, C10BX09) in (last 4 months of) current year (2012)
Blood pressure lowering drugs	
11. The percentage of patients with T2D between 18 and 70 years with an elevated systolic blood pressure in the previous year, that started with antihypertensives or that reached the systolic blood pressure target level	· Elevated systolic blood pressure: most recent measure in previous year (2011) >140 mmHg · Target level systolic blood pressure: most recent measure in current year (2012) ≤140 mmHg · Start antihypertensives: o No prescriptions (ATC codes: C02, C03, C07, C08, C09) in (last 4 months of) previous year (2011) and o ≥1 prescriptions (ATC codes: C02, C03, C07, C08, C09) in (last 4 months of) current year (2012)

Table S5.2: Operational definitions for selected prescribing quality indicators (continued)

Overall	**Operationalization**
12. The percentage of patients with T2D between 18 and 70 years treated with monotherapy antihypertensives and with an elevated systolic blood pressure in the previous year, that is intensified with antihypertensives or that reached the systolic blood pressure target level	· Elevated blood pressure: most recent measure in previous year (2011) >140 mmHg · Target level blood pressure: most recent measure in current year (2012) ≤140 mmHg · Intensified antihypertensive treatment: o ≥1 prescription for 2 drug classes (ATC codes: C02, C03, C07, C08, C09, excluding ATC codes for combinations) in (last 4 months of) previous year (2011) or o ≥1 prescription for combinations (ATC codes: C03EA01, C03EA03, C07BB02, C07BB07, C07CA03, C07CB03, C09B, C09D, C09XA52) in (last 4 months of) current year (2012)
Albuminuria lowering drugs	
13. The percentage of patients with T2D 18 years or older treated with two or more antihypertensives that is prescribed an ACE-i or ARB	· Two or more antihypertensives: o ≥ 1 prescriptions for 2 drug classes (ATC codes: C02, C03, C07, C08, C09, excluding ATC codes for combinations) in (last 4 months of) current year (2012) or o ≥1 prescription for combinations (ATC codes: C03EA01, C03EA03, C07BB02, C07BB07, C07CA03, C07CB03, C09B, C09D, C09XA52) in (last 4 months of) current year (2012) · ACE-i/ARB therapy: ≥1 prescriptions (ATC codes: C09A, C09B, C09C, C09D) in (last 4 months of) current year (2012)
14. The percentage of patients with T2D between 18 and 70 years with micro- or macro-albuminuria in the previous year, that started with an ACE-i or ARB or that returned to normo-albuminuria	· Micro- or macro-albuminuria: most recent ACR measurement in previous year (2011): >2.5 mg/mmol for males and >3.5 mg/mmol for females · Normo-albuminuria: most recent ACR measurement in current year (2012): ≤2.5 for males and ≤3.5 for females · Start ACE-i/ARB treatment: o No prescriptions (ATC codes: C09A, C09B, C09C, C09D) in (last 4 months of) previous year (2011) and o ≥ 1 prescription (ATC codes: C09A, C09B, C09C, C09D) in (last 4 months of) current year (2012)
15. The percentage of patients with T2D 18 years or older treated with antihypertensives and with micro- or macro-albuminuria that is prescribed an ACE-i or ARB	· Micro- or macro-albuminuria: most recent ACR measurement in previous year (2011): >2.5 mg/mmol for males and >3.5 mg/mmol for females · Antihypertensive treatment: ≥1 prescription (ATC codes: C02, C03, C07, C08, C09) in (last 4 months of) current year (2012) · ACE-i/ARB treatment: ≥1 prescription (ATC codes: C02, C03, C07, C08, C09) in (last 4 months of) current year (2012)

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Table S5.2: Operational definitions for selected prescribing quality indicators (continued)

Overall	**Operationalization**
16. The percentage of patients with T2D 18 years or older that started with an ACE-i among all patients that started with RAAS treatment	· Start RAAS treatment: o No prescriptions (ATC code: C09) in (last 4 months of) previous year (2011) and o ≥1 prescription (ATC code: C09) in (last 4 months of) current year (2012) · Start ACE-i treatment: o No prescriptions (ATC code: C09A, C09B) in (last 4 months of) current year (2012) and o ≥1 prescription (ATC codes: C09A, C09B) in (last 4 months of) current year (2012)
Medication safety	
17. The percentage of patients with T2D 18 years or older treated with SU-derivatives that is prescribed glibenclamide	· SU-derivate treatment: ≥1 prescriptions (ATC codes: A10BB, A10BD02, A10BD04, A10BD06) in (last 4 months of) current year (2012) · Glibenclamide therapy: ≥1 prescriptions (ATC code A10BB01) in (last 4 months of) current year (2012)
18. The percentage of patients with T2D 18 years or older with an eGFR <30 ml/min/1.73m^2 that is prescribed metformin	· Metformin treatment: ≥1 prescriptions (ATC codes: A10BA02, A10BD02, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD17, A10BD18) in (last 4 months of) current year (2012) · eGFR <30 ml/min/1.73m^2 based on CKD-EPI formula using last serum creatinin measurement in current year (2012)
19. The percentage of patients with T2D 80 years or older with a normal HbA_{1c} level that is prescribed two or more glucose lowering drugs	· Normal HbA_{1c} level: most recent measurement in current year (2012) <53 mmol/mol · Two or more glucose lowering drugs: o ≥1 prescription for 2 drug classes (ATC codes: A10A, A10BA, A10BB, A10BF, A10BG, A10BH, A10BX) in (last 4 months of) current year (2012) or o ≥1 prescription for drug class (ATC code: A10BD) in (last 4 months of) current year (2012)
20. The percentage of patients with T2D 18 years or older treated with RAAS inhibitors that is prescribed a combination of an ACE-i and ARB (dual RAAS blockade)	· RAAS treatment: ≥1 prescription (ATC code: C09) in the last 4 months of current year (2012) · Combination ACE-i and ARB: o ≥1 prescription (ATC codes: C09A, C09B) in (last 4 months of) current year (2012) and o ≥1 prescription (ATC codes: C09C, C09D) in (last 4 months of) current year (2012)

T2D: type 2 diabetes; ICPC: International Classification of Primary Care; HbA_{1c}: glycated haemoglobin; ATC: Anatomical Therapeutic Chemical Classification System; eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; SU-derivative: sulphonylurea derivatives; LDL-cholesterol: low-density lipoprotein-cholesterol; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; ACR: albumin/creatinine ratio; RAAS: renin-angiotensin-aldosterone system.

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Table S5.3A: Sensitivity analysis including patients with missing measurements in previous year (2011) in start and intensification indicators in ZODIAC

List of indicators
Glucose lowering drugs
1. The percentage of patients with T2D between 18 and 70 years with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that started with glucose lowering drugs or that reached the HbA_{1c} target level (≤53 mmol/mol)
2. The percentage of patients with T2D between 18 and 70 years treated with monotherapy metformin and with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that is intensified with glucose lowering drugs or that reached the HbA_{1c} target level (≤53 mmol/mol)
3. The percentage of patients with T2D between 18 and 70 years treated with two or more non-insulin glucose lowering drugs and with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that started with insulin or that reached the HbA_{1c} target level (≤53 mmol/mol)
Lipid lowering drugs
9. The percentage of patients with T2D between 18 and 80 years with an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that started with a statin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)
10. The percentage of patients with T2D between 18 and 80 years treated with simvastatin and with an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that switched to atorvastatin or rosuvastatin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)
Blood pressure lowering drugs
11. The percentage of patients with T2D between 18 and 70 years with an elevated systolic blood pressure (>140 mmHg) in the previous year, that started with antihypertensives or that reached the systolic blood pressure target level (≤140 mmHg)
12. The percentage of patients with T2D between 18 and 70 years treated with monotherapy antihypertensives and with an elevated systolic blood pressure (>140 mmHg) in the previous year, that is intensified with antihypertensives or that reached the systolic blood pressure target level (≤140 mmHg)
Albuminuria lowering drugs
14. The percentage of patients with T2D between 18 and 70 years with micro- or macro-albuminuria[†] in the previous year, that started with an ACE-i or ARB or that returned to normo-albuminuria[†]

ZODIAC: Zwolle Outpatient Diabetes project Integrating Available Care; T2D: type 2 diabetes; HbA_{1c}: glycated haemoglobin; LDL-cholesterol: low-density lipoprotein-cholesterol; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker.

	ZODIAC without missings (original analysis)					ZODIAC with missings (sensitivity analysis)				
	Outcome score (%)	Nominator/denominator	Percentage of eligible patients	N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison	Outcome score (%)	Nominator/denominator	Percentage of eligible patients	N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison
	80.9	178/ 220	0.4	60	15,323	97.1	7,288/ 7,507	13.2	11	83
	66.1	846/ 1,280	2.3	87	3,821	68.7	1,028/ 1,496	2.6	83	3,136
	42.9	687/ 1,603	2.8	95	3,335	44.7	777/ 1,739	3.1	95	3,102
	33.1	1,436/ 4,342	7.6	86	1,113	64.4	9,513/ 14,773	26.0	89	339
	45.5	1,587/ 3,488	6.1	96	1,552	50.2	2,058/ 4,099	7.2	97	1,332
	63.4	724/ 1,142	2.0	90	4,435	88.6	7,481/ 8,441	14.9	39	261
	57.1	816/ 1,428	2.5	95	3,743	58.2	901/ 1,549	2.7	94	3,429
	61.0	326/ 534	0.9	95	9,719	92.5	7,124/ 7,700	13.6	27	197

† Micro/macro-albuminuria is defined as an albumin/creatinine ratio ≥2.5 mg/mmol for males and ≥3.5 mg/mmol for females. Normo-albuminurie is defined as an albumin/creatinine ratio <2.5 mg/mmol for males and <3.5 mg/mmol for females.

Table S5.3B: Sensitivity analysis including patients with missing measurements in previous year (2011) in start and intensification indicators in GIANTT

List of indicators
Glucose lowering drugs
1. The percentage of patients with T2D between 18 and 70 years with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that started with glucose lowering drugs or that reached the HbA_{1c} target level (≤53 mmol/mol)
2. The percentage of patients with T2D between 18 and 70 years treated with monotherapy metformin and with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that is intensified with glucose lowering drugs or that reached the HbA_{1c} target level (≤53 mmol/mol)
3. The percentage of patients with T2D between 18 and 70 years treated with two or more non-insulin glucose lowering drugs and with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that started with insulin or that reached the HbA_{1c} target level (≤53 mmol/mol)
Lipid lowering drugs
9. The percentage of patients with T2D between 18 and 80 years with an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that started with a statin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)
10. The percentage of patients with T2D between 18 and 80 years treated with simvastatin and with an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that switched to atorvastatin or rosuvastatin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)
Blood pressure lowering drugs
11. The percentage of patients with T2D between 18 and 70 years with an elevated systolic blood pressure (>140 mmHg) in the previous year, that started with antihypertensives or that reached the systolic blood pressure target level (≤140 mmHg)
12. The percentage of patients with T2D between 18 and 70 years treated with monotherapy antihypertensives and with an elevated systolic blood pressure (>140 mmHg) in the previous year, that is intensified with antihypertensives or that reached the systolic blood pressure target level (≤140 mmHg)
Albuminuria lowering drugs
14. The percentage of patients with T2D between 18 and 70 years with micro- or macro-albuminuria[†] in the previous year, that started with an ACE-i or ARB or that returned to normo-albuminuria[†]

GIANTT: Groningen Initiative to Analyse Type 2 diabetes Treatment; T2D: type 2 diabetes; HbA_{1c}: glycated haemoglobin; LDL-cholesterol: low-density lipoprotein-cholesterol; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker.

GIANTT without missings (original analysis)					GIANTT with missings (sensitivity analysis)				
Outcome score (%)	Nominator/denominator	Percentage of eligible patients	N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison	Outcome score (%)	Nominator/denominator	Percentage of eligible patients	N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison
73.1	174/ 238	0.9	76	8,353	83.7	497/ 594	2.3	53	2,326
61.1	618/ 1,012	3.8	92	2,376	64.4	796/ 1,236	4.7	89	1,876
38.8	446/ 1,150	4.4	92	2,088	40.3	512/ 1,271	4.8	93	1,914
32.1	1,100/ 3,429	13.0	84	643	35.1	1,610/ 4,588	17.4	88	502
46.3	1,105/ 2,389	9.1	96	1,053	54.4	1,873/ 3,443	13.1	96	729
56.9	562/ 988	3.8	95	2,511	66.1	1,056/ 1,597	6.1	87	1,419
55.3	588/ 1,064	4.0	95	2,350	58.4	832/ 1,424	5.4	94	1,725
59.5	132/ 222	0.8	93	10,980	90.4	1,524/ 1,686	6.4	34	521

† Micro/macro-albuminuria is defined as an albumin/creatinine ratio ≥2.5 mg/mmol for males and ≥3.5 mg/mmol for females. Normo-albuminurie is defined as an albumin/creatinine ratio <2.5 mg/mmol for males and <3.5 mg/mmol for females.

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Table S5.4: Sensitivity analysis using any medication in a year instead of prescribed in the last four months of the year in GIANTT

List of indicators
Glucose lowering drugs
1. The percentage of patients with T2D between 18 and 70 years with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that started with glucose lowering drugs or that reached the HbA_{1c} target level (≤53 mmol/mol)
2. The percentage of patients with T2D between 18 and 70 years treated with monotherapy metformin and with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that is intensified with glucose lowering drugs or that reached the HbA_{1c} target level (≤53 mmol/mol)
3. The percentage of patients with T2D between 18 and 70 years treated with two or more non-insulin glucose lowering drugs and with an elevated HbA_{1c} level (>53 mmol/mol) in the previous year, that started with insulin or that reached the HbA_{1c} target level (≤53 mmol/mol)
4. The percentage of patients with T2D 18 years or older that started with metformin among all starters of oral glucose lowering drugs
5. The percentage of patients with T2D 18 years or older treated with glucose lowering drugs that is prescribed metformin
6. The percentage of patients with T2D 18 years or older treated with two non-insulin glucose lowering drugs that is prescribed a combination of metformin and an SU-derivative
7. The percentage of patients with T2D 18 years or older that started with gliclazide among all starters of an SU-derivative
Lipid lowering drugs
8. The percentage of patients with T2D between 55 and 80 years that is prescribed a statin
9. The percentage of patients with T2D between 18 and 80 years with an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that started with a statin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)
10. The percentage of patients with T2D between 18 and 80 years treated with simvastatin and with an elevated LDL-cholesterol level (>2.5 mmol/l) in the previous year, that switched to atorvastatin or rosuvastatin or that reached the LDL-cholesterol target level (≤2.5 mmol/l)
Blood pressure lowering drugs
11. The percentage of patients with T2D between 18 and 70 years with an elevated systolic blood pressure (>140 mmHg) in the previous year, that started with antihypertensives or that reached the systolic blood pressure target level (≤140 mmHg)
12. The percentage of patients with T2D between 18 and 70 years treated with monotherapy antihypertensives and with an elevated systolic blood pressure (>140 mmHg) in the previous year, that is intensified with antihypertensives or that reached the systolic blood pressure target level (≤140 mmHg)

	Last 4 months (original analysis)					Any use (sensitivity analysis)				
	Outcome score (%)	Nominator/ denominator	Percentage of eligible patients	N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison	Outcome score (%)	Nominator/ denominator	Percentage of eligible patients	N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison
	73.1	174/ 238	0.9	76	8,353	76.6	111/ 145	0.6	70	12,518
	61.1	618/ 1,012	3.8	92	2,376	62.7	582/ 928	3.5	90	2,548
	38.8	446/ 1150	4.4	92	2,088	40.9	492/ 1,202	4.6	93	2,034
	78.7	841/ 1,069	4.1	65	1,688	84.9	685/ 807	3.1	50	1,608
	86.3	14,984/ 17,353	65.9	46	69	87.3	15,757/ 18,054	68.6	43	63
	87.0	4,865/ 5,589	21.2	44	205	87.9	5,305/ 6,038	22.9	41	179
	67.5	666/ 986	3.7	85	2,249	68.0	633/ 931	3.5	84	2,364
	71.7	13,123/ 18,301	69.5	78	113	76.2	13,937/ 18,301	69.5	70	101
	32.1	1,100/ 3,429	13.0	84	643	33.3	1,013/ 3,040	11.5	86	740
	46.3	1,105/ 2,389	9.1	96	1,053	48.4	1,373/ 2,837	10.8	96	891
	56.9	562/ 988	3.8	95	2,511	56.9	509/ 894	3.4	95	2,774
	55.3	588/ 1,064	4.0	95	2,350	54.2	556/ 1,026	3.9	96	2,447

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Table S5.4: Sensitivity analysis using any medication in a year instead of prescribed in the last four months of the year in GIANTT (continued)

List of indicators
Albuminuria lowering drugs
13. The percentage of patients with T2D 18 years or older treated with two or more antihypertensives that is prescribed an ACE-i or ARB
14. The percentage of patients with T2D between 18 and 70 years with micro- or macro-albuminuria† in the previous year, that started with an ACE-i or ARB or that returned to normo-albuminuria†
15. The percentage of patients with T2D 18 years or older treated with antihypertensives and with micro- or macro-albuminuria† that is prescribed an ACE-i or ARB
16. The percentage of patients with T2D 18 years or older that started with an ACE-i among all patients that started with RAAS treatment
Medication safety
17. The percentage of patients with T2D 18 years or older treated with SU-derivatives that is prescribed glibenclamide
20. The percentage of patients with T2D 18 years or older treated with RAAS inhibitors that is prescribed a combination of an ACE-i and ARB (dual RAAS blockade)

GIANTT: Groningen Initiative to Analyse Type 2 diabetes Treatment; T2D: type 2 diabetes; HbA_{1c}: glycated haemoglobin; SU-derivative: sulphonylurea derivatives; LDL-cholesterol: low-density lipoprotein-cholesterol; ACE-i: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-II-receptor-blocker; RAAS: renin-angiotensin-aldosterone system.
† Micro/macro-albuminuria is defined as an albumin/creatinine ratio ≥2.5 mg/mmol for males and ≥3.5 mg/mmol for females. Normo-albuminuria is defined as an albumin/creatinine ratio <2.5 mg/mmol for males and <3.5 mg/mmol for females.

	Last 4 months (original analysis)					Any use (sensitivity analysis)				
	Outcome score (%)	Nominator/ denominator	Percentage of eligible patients	N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison	Outcome score (%)	Nominator/ denominator	Percentage of eligible patients	N eligible patients needed for comparison	Minimal number of T2D patients needed for reliable comparison
	87.4	12,789/ 14,627	55.6	43	77	88.7	13,817/ 15,573	59.2	39	65
	59.5	132/ 222	0.8	93	10,980	62.0	124/ 200	0.8	91	11,912
	84.5	2,451/ 2,901	11.0	51	457	87.1	2,604/ 2,991	11.4	44	381
	70.5	920/ 1,305	5.0	80	1,612	79.9	908/ 1,137	4.3	62	1,431
	2.1	163/ 7,859	29.9	781	2,614	2.2	187/ 8,644	32.8	814†	2,476
	3.2	502/ 15,714	59.7	1,189	1,991	5.0	835/ 16,657	63.3	74‡	116

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Appendix 5: Supplemental data chapter 6

Table S6.1: Definition of comorbidities, which were documented in the medical records by means of the ICPC or short text prescriptions which were manually coded in GIANTT

Comorbidity	Short text prescriptions	ICPC codes
Cardiovascular disease	Ischaemic heart disease with angina	K74
	Acute myocardial infarction	K75
	Ischaemic heart disease without angina	K76
	Heart valve disease	K83
	Other heart disease	K84
	Transient cerebral ischeamia	K89
	Stroke/cerebrovascular accident	K90
	Left ventricular hypertrophy	
	Coronary artery bypass grafting	
	Percutaneous coronary angioplasty	
Peripheral vascular disease	Cerebrovascular disease	K91
	Atherosclerosis/PVD	K92
	Peripheral artery bypass grafting	
	Percutaneous transluminal angioplasty	
Renal complications	Congenital anomaly urinary tract	U85
	Glomerulonephritis/nephrosis	U88
	Orthostatic albumin/proteinuria	U90
	Renal failure	U99.1
	Renal hyperplasia	U99.2
	Renal hydronephrosis	U99.3
	Dialysis	
	Kidney transplantation	
Diabetic complications	Retinopathy	F83
	Peripheral diabetic angiopathy	K99.6
	Diabetic neuropathy	N94.2
	Nephropathy	
	Diabetic foot	
	Amputation of toes and/or feet	
Malignancies	Malignancy of unknown primary site	A79
	Hodgkin's disease	B72
	Leukemia	B73
	Other malignancies blood/lymphatic system	B74
	Stomach malignancy	D74
	Colon/rectum malignancy	D75
	Pancreatic malignancy	D76

Table S6.1: Definition of comorbidities, which were documented in the medical records by means of the ICPC or short text prescriptions which were manually coded in GIANTT (continued)

Comorbidity	Short text prescriptions	ICPC codes
	Other nonspecified malignancy digestive system	D77
	Neoplasm eye/adnexa	F74.1
	Ear malignancy	H75.1
	Benign neoplasm cardiovascular system	K72.1
	Neoplasm musculoskeletal	L71.1
	Nervous system malignancy	N74
	Bronchus/lung malignancy	R84
	Other respiratory malignancy	R85
	Skin/subcutaneous malignancy	S77
	Thyroid malignancy	T71
	Kidney malignancy	U75
	Bladder malignancy	U76
	Other urinary tract malignancy	U77
	Cervic uteri malignancy	X75
	Breast malignancy	X76
	Other female genital malignancy	X77
	Prostate malignancy	Y77
	Other male genital malignancy	Y78
Psychological comorbidities	Dementia/Alzheimer	P70
	Other organic psychosis	P71
	Schizophrenia	P72
	Affective psychosis	P73
	Anxiety disorder	P74
	Histeria/hypochondria	P75
	Depression	P76
	Suicide attempt	P77
	Neurasthenia/surmenage	P78
	Other neurotis	P79
	Personality/character disorder	P80
	Mental/intellectual retardation	P98
	Other/non specified psychosis	P99

GIANTT: Groningen Initiative to Analyse Type 2 diabetes Treatment; ICPC: International Classification of Primary Care

Table S6.2: Selected confounders in fully adjusted model per indicator

			Patient characteristics (p-values)													
Ind	**Effect size**	**95% CI**	**Baseline risk factor**	**Age**	**Gender**	**Diabetes duration**	**Time between indicator and outcome date**	**BMI**	**Smoking**	**CVD**	**PVD**	**Renal complications**	**Diabetic complications**	**Malignancy**	**Psychological comorbidities**	**N of selected patient characteristics**
1	-5.2	-9.0; -1.4	<0.001	0.149												2
2	-8.5	-9.9; -7.2	<0.001	0.019		<0.001	0.001	0.167			0.20		0.134		0.159	8
3	-8.9	-10.1; -7.5	<0.001	0.002		<0.001	0.001									4
4	-0.30	-0.33; -0.27	<0.001	0.018	<0.001	0.060	<0.001		0.019	0.036			0.010	0.195		9
5	-0.97	-1.03; -0.90	<0.001	0.500					0.163							3
6	-0.62	-0.70; -0.54	<0.001	0.087	0.169	0.1819	0.157	0.1454	0.069		0.078					8
7	-8.4	-10.4; -6.4	<0.001	0.009	0.042					0.122	0.035					5
8	-9.5	-11.5; -7.5	<0.001	0.040				0.102			0.154	0.037			0.081	6
9	0.11†	0.04-0.34†		0.074		0.137					0.183	0.024		0.089	0.107	6
10	0.94†	0.75-1.18†	<0.001	<0.001	<0.001	<0.001	0.068	0.141	<0.001			<0.001				8
11	1.22†	0.92-1.62†	<0.001	0.004	<0.001				0.001	0.158	0.075	0.011		0.010	0.144	9

Ind: indicator; 95% CI: 95% confidence interval; BMI: body mass index; CVD: cardiovascular disease comorbidity, PVD: peripheral disease comorbidity; RAAS: renin-angiotensin-aldosterone system.

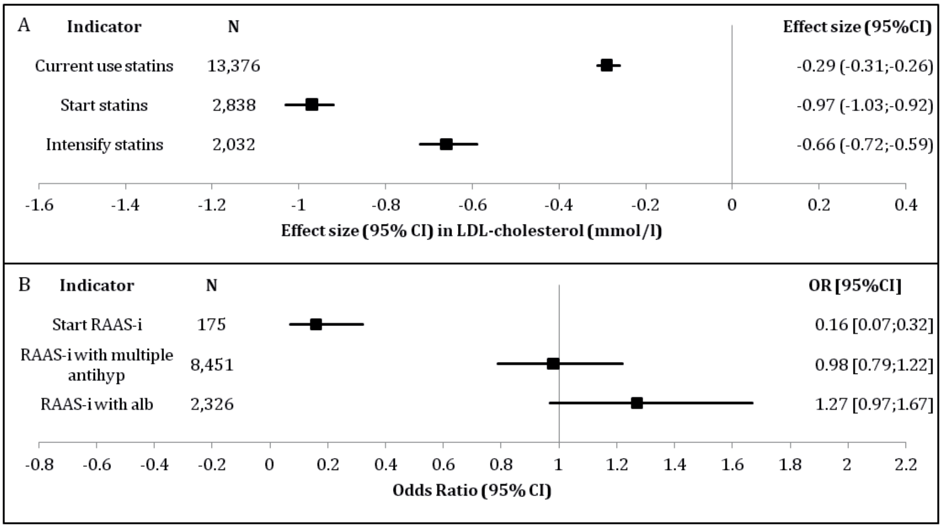
† Odds ratios with 95% CI intervals for logistic regression models.

Ind 1: start of glucose lowering drugs; Ind2: intensification with glucose lowering drugs after metformin monotherapy; Ind 3: intensification with insulin after two or more glucose lowering drugs; Ind 4: current prescription of statins; Ind 5: start of statins; Ind 6: intensification of statins; Ind 7: start of antihypertensives; Ind 8: intensification of antihypertensives; Ind 9: start of RAAS inhibitors; Ind 10: current use of RAAS inhibitors among multiple antihypertensive use; Ind 11: current use of RAAS inhibitors with albuminuria.

Table S6.3: Odds ratios for albuminuria in 2013 per age category for indicator on current use of renin-angiotensin-aldosterone system inhibitors when multiple antihypertensives are used

Age categories	Odds ratio	95% Confidence intervals
<63.1 years	1.34	0.76-2.38
63.1-69.5 years	1.01	0.59-1.72
69.5-76.5 years	1.00	0.63-1.60
≥76.5 years	0.80	0.57-1.12

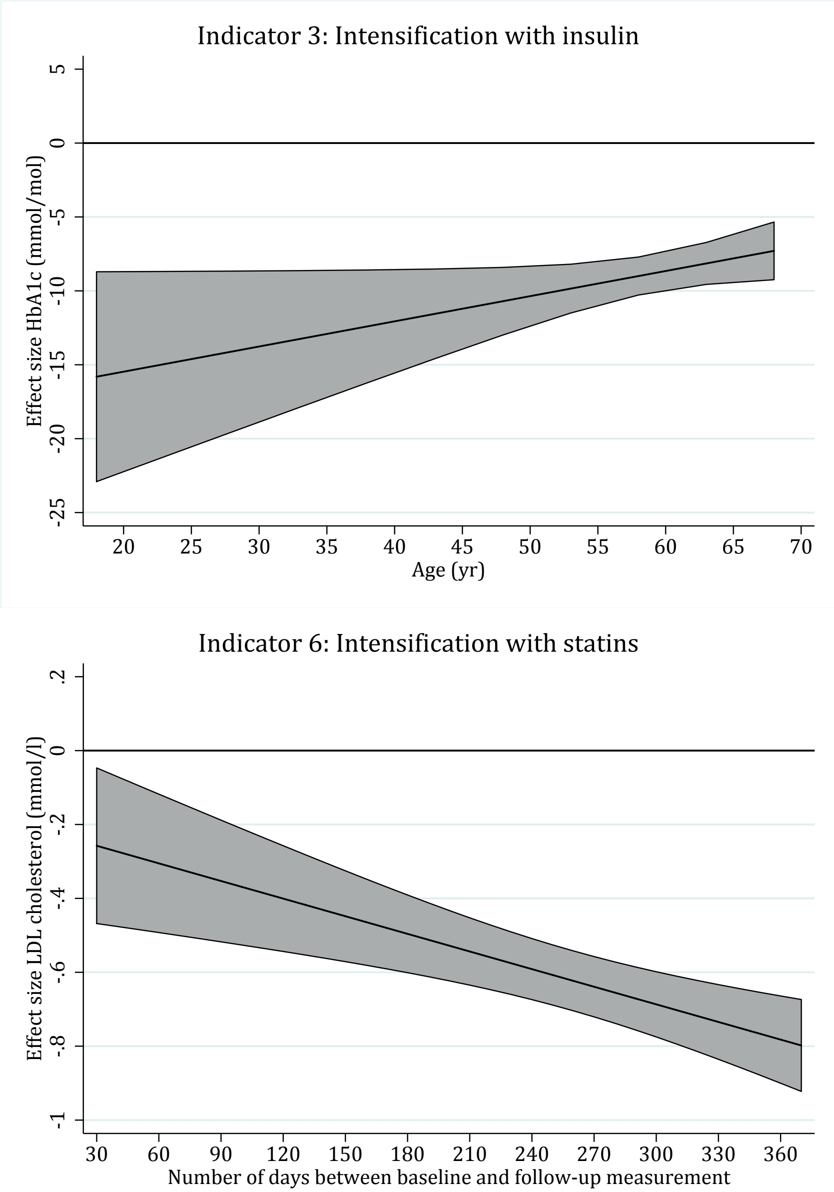
Figure S6.1: Sensitivity analysis of indicators on statin (A) and RAAS inhibitors (B) using an allowed time period between indicator and outcome date of 548 days (1.5 years)



95%CI: 95% confidence intervals; LDL-cholesterol: low-density lipoprotein-cholesterol; OR: odds ratio; RAAS-i: RAAS inhibitors; antihyp: antihypertensives; alb: albuminuria.

A

Figure S6.2: Indicators with significant effect modification of age (A) and time between measurements (B)



HbA_{1c}: glycated haemoglobin; LDL-cholesterol: low-density lipoprotein-cholesterol
Predictive value of the indicator focusing on intensification with insulin on HbA_{1c} levels on the y-axis with increasing age on the x-axis (A) and of the indicator focusing on intensification with statins on LDL-cholesterol on the y-axis with increasing time between indicator and follow-up measurement of LDL-cholesterol (B).

Curriculum vitae

Kirsten Smits was born on August 17th, 1989 in Steinheim, Germany. After finishing secondary school in 2007, she started her study, Nutrition and Health at the Wageningen University. In 2011, she obtained her Bachelor's degree and continued with a master Nutrition and Health specialising in Epidemiology and Public Health at the Wageningen University. During her master program, she wrote her master thesis focusing on the association of fish fatty acids with cardiovascular disease in healthy people, patients with prior myocardial infarction and patients with diabetes. In 2012, she travelled to Pittsburgh, United States of America for an internship of 6 months at Pittsburgh University. There she studied the relation between vitamin E and vitamin C with coronary artery disease and haptoglobin genotype in diabetes patients. She obtained her masters degree in 2013.

From March 2014 to August 2017, she worked as a PhD candidate at the department of Clinical Pharmacy and Pharmacology of the University Medical Center Groningen. Her PhD-project focused on developing and validating prescribing quality indicators to assess the quality of chronic kidney disease and diabetes type 2 care.

Since October 2017, she works as a postdoctoral researcher at the department of Quality and Safety of Oral Health Care at the Radboud university medical center. Her work is focused on quality indicators for assessing quality of oral health care, as well as finding links between nutritional aspects and oral health and patient perceptions of integrated health care.

Dankwoord

Tijdens mijn studie raakte ik vrij snel geïnteresseerd in het doen van onderzoek en specifiek in de epidemiologische hoek. Deze interesse is verder gegroeid tijdens mijn masterthesis bij de Wageningen Universiteit onder begeleiding van dr. Sabita Soedemah-Muthu en daarna tijdens mijn afstudeerstage aan Pittsburgh University, Pennsylvania, USA onder gezamenlijke begeleiding van Prof. dr. Trevor Orchard en dr. Sabita Soedemah-Muthu. Sabita, bedankt voor je begeleiding tijdens mijn master periode en je enthousiasme voor onderzoek dat je op mij hebt weten over te brengen. Mede hierdoor wilde ik graag promoveren en beginnen aan een carrière binnen de academische onderzoekswereld. Deze mogelijkheid vond ik in Groningen bij de afdeling Klinische Farmacie en Farmacologie van het Universitair Medisch Centrum Groningen.

Dit proefschrift had ik echter niet kunnen schrijven zonder de hulp en ondersteuning van veel mensen. Een aantal wil ik graag in het bijzonder bedanken.

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Prof. dr. H.J.G. Bilo: Beste Henk, na onze eerste ontmoeting was ik een beetje ontdaan, maar al snel daarna ben ik je directheid en kritische blik gaan waarderen. Ondanks dat je ontzettend druk was, wist je altijd wel tijd te vinden voor mij en mijn project. Dank je wel voor je inzet, je input, en je kritische noot.

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